EXAMINING CANADIAN SMOKING RELATED BEHAVIOURS AND ASSOCIATED HEALTH OUTCOMES

A Thesis Submitted to the College of Graduate and Postdoctoral Studies
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By

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ABSTRACT

Tobacco use is the leading cause of premature death worldwide. To address the growing tobacco epidemic, the World Health Organization introduced the Framework Convention on Tobacco Control. However, there has been an evolution in tobacco products with flavoured tobacco and electronic nicotine delivery systems such as electronic cigarettes (e-cigarettes). Furthermore, the tobacco industry continues to disproportionately target vulnerable populations to recruit new users. As such, it is critical to be aware of paradigm shifts in Canadian smoking behaviours to identify vulnerable populations and to assess the potential harms related to changing smoking behaviours.

When examining flavoured tobacco use the prevalence was elevated among Canadian high school students and being males, exposed to peer pressure and having increased weekly spending money were identified as significant determinants of flavoured tobacco use.

The lesbian, gay and bisexual (LGB) population is vulnerable to tobacco use due to intrinsic factors, social factors and targeted tobacco advertising. Results of this study showed the prevalence of smoking was higher in the Canadian LGB population compared to national rates. There was a significant association between sexual orientation and smoking status for lesbians and bisexuals compared to heterosexuals, but no significant association between gay and bisexuals and heterosexual males.

Health effects of e-cigarettes have not been well characterized. Using the Canadian Community Health Survey, an exploratory study examining the association between past 30-day e-cigarette use and chronic obstructive pulmonary disease (COPD) was examined. A sex-based interaction effect with female e-cigarette users reporting higher rates of COPD compared to males was identified. Furthermore, dual use behaviour was most strongly associated with COPD.

In the systematic review and meta-analysis examining if e-cigarette use among baseline never conventional tobacco users predicted tobacco initiation at follow up, the meta-analysis indicated ever e-cigarette users were significantly more likely to initiate tobacco use and current (past 30-day) tobacco use compared to never e-cigarette users.

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DEDICATION

I dedicate this thesis to my dear parents for their unconditional love, support and sacrifices.

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LIST OF ABBREVIATIONS

E-Cigarette	Electronic Cigarette
ENDS	Electronic Nicotine Delivery System
WHO	World Health Organization
WHO FCTC	World Health Organization Framework Convention on Tobacco Control
COPD	Chronic Obstructive Pulmonary Disease
LGB	Lesbian, Gay, Bisexual
CCHS	Canadian Community Health Survey
MTPTF	Multiple Tobacco Product use Theoretical Framework
YSS	Youth Smoking Survey
VIF	Variance Inflation Factor
TOL	Tolerance
OR	Odds Ratio
aOR	Adjusted Odds Ratio
RR	Relative Risk (Risk Ratio)
aRR	Adjusted Relative Risk (Risk Ratio)
SKY-RDC	Saskatchewan Research Data Centre
ETS	Environmental Tobacco Smoke
SES	Socio-Economic Status
95% CI	95% Confidence Interval

CHAPTER 1: INTRODUCTION TO SMOKING RELATED BEHAVIOURS

1.1 Background

1.1.1 Scope and trends in tobacco and tobacco-related product use

Tobacco use is the leading cause of premature death worldwide.[1] The negative health outcomes of tobacco use have been well characterized and are numerous such as: cancers, cardiovascular and cerebrovascular accidents, lung diseases (i.e. chronic obstructive pulmonary disease), and autoimmune disorders.[2] In 2005, the World Health Organization (WHO) introduced the WHO Framework Convention on Tobacco Control (WHO FCTC) to combat the tobacco epidemic.[3] This resolution, which is a global treaty that outlines comprehensive and multisectoral tobacco control strategies, plans and programs encompassing aspects related to policies of taxation, exposure to tobacco smoke, contents of tobacco cigarettes, packaging and labelling, health promotion and education, restrictions in advertising, sales to minors, and measures promoting tobacco cessation.[3] While in the 2018 WHO report conventional tobacco control measures have become more readily adopted, there is a lag in developing policies about smokeless tobacco, water pipe and electronic nicotine delivery systems (ENDS).[3] Globally, the WHO is reporting decreasing trends in conventional tobacco use in over half the countries (though 13% of the countries reported an increase in tobacco use), while 39% reported decreasing trends solely among adults.[3] It is estimated that the prevalence of current tobacco smokers (past 30-day smokers) will continue to decrease overall among all countries stratified by World Bank income group (Figure 1.1); however, males in high income countries have dramatically declined from having the highest prevalence of current smoking to the second lowest in twenty years (Figure 1.2).[3] When examining the female prevalence of current tobacco use, while overall rates are decreasing, it should be noted that females in high income countries continue to have a significantly higher prevalence of current tobacco use compared to all other groups (Figure 1.3)[3] suggesting societal and environmental factors may be influencing their smoking behaviours.

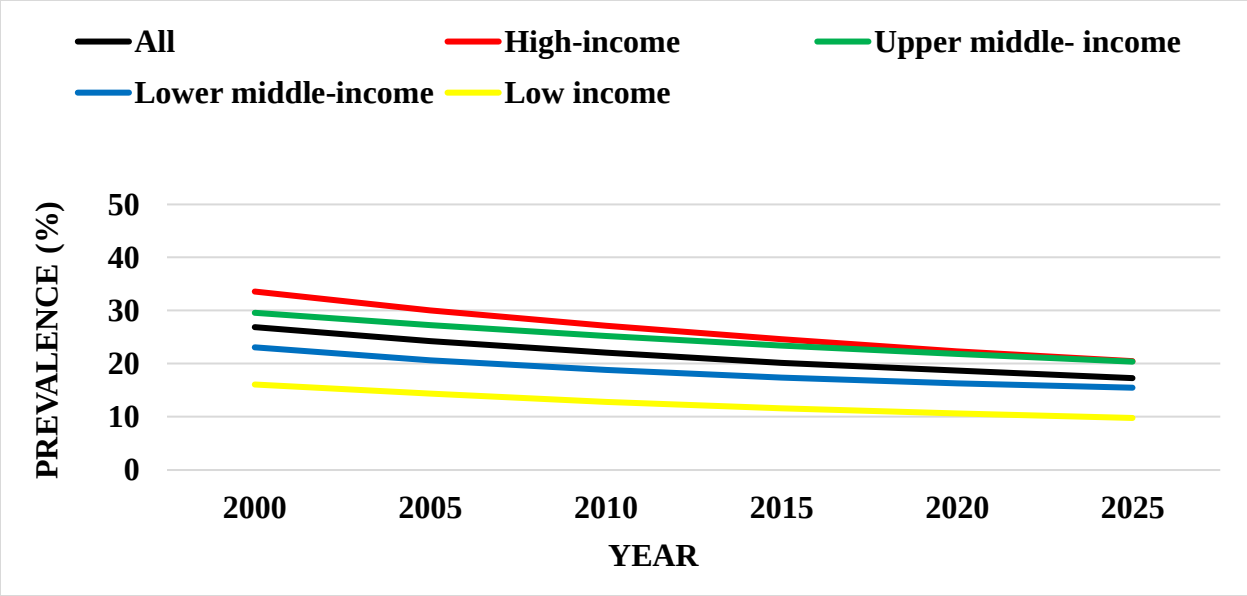

Figure 1.1: Global trends in current tobacco smoking prevalence and future estimates, ages 15+ by countries stratified by World Bank income groups. Figure adapted from (FCTC WHO, 2018).[3]

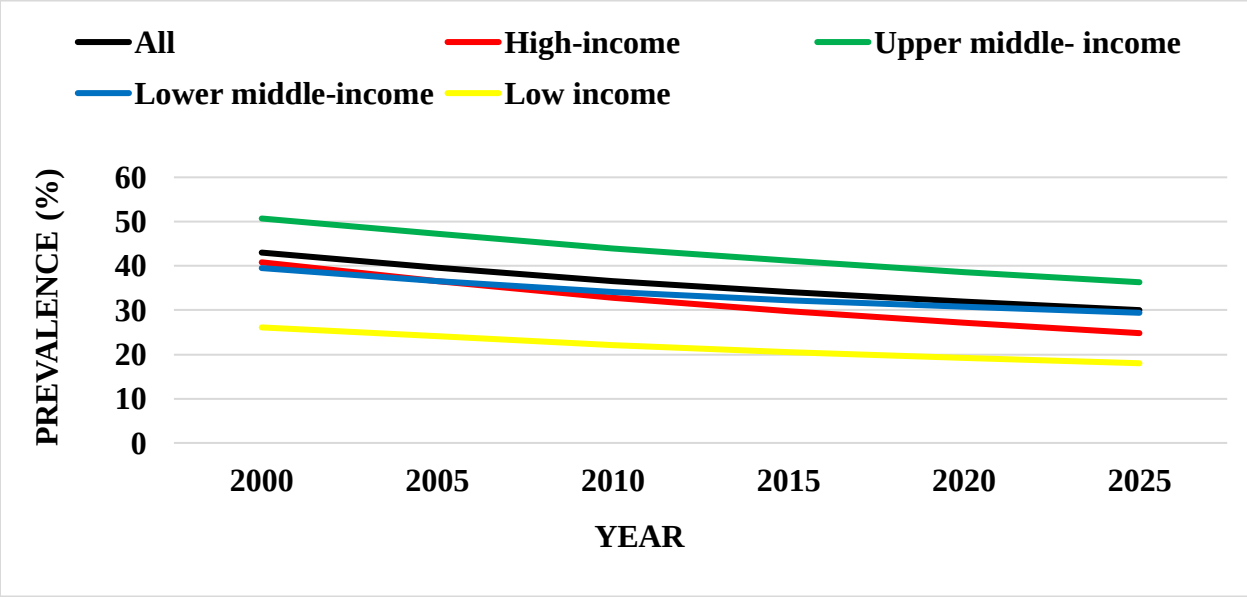

Figure 1.2: Global trends in male current tobacco smoking prevalence and future estimates, ages 15+ by countries stratified by World Bank income groups. Figure adapted from (FCTC WHO, 2018).[3]

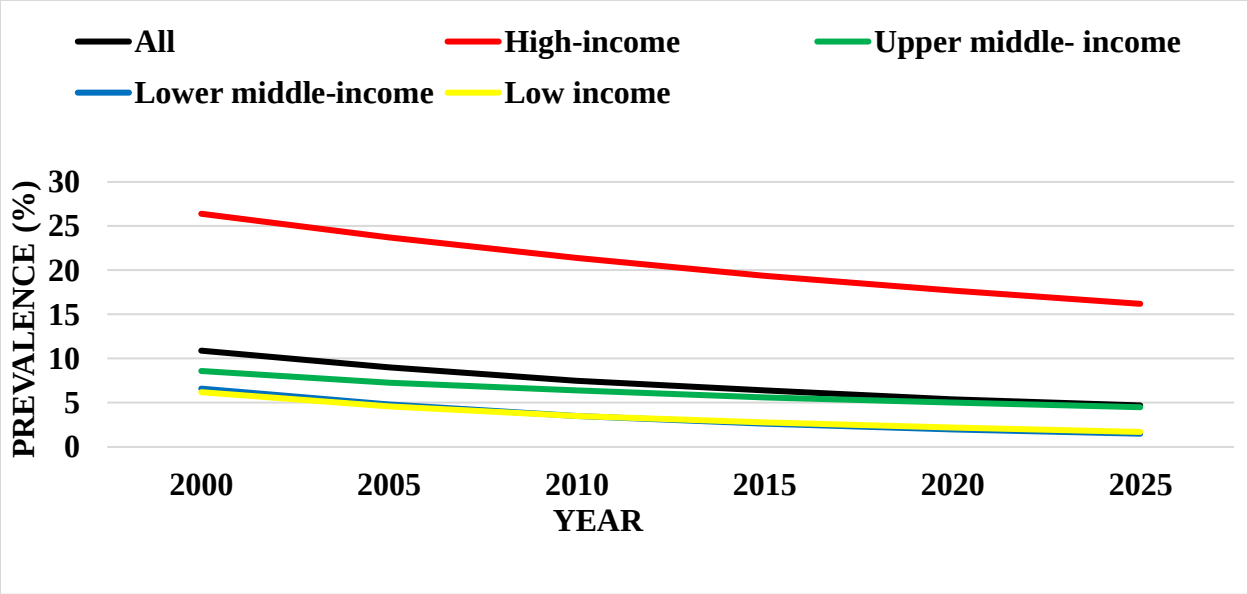

Figure 1.3: Global trends in female current tobacco smoking prevalence and future estimates, ages 15+ by countries stratified by World Bank income groups. Figure adapted from (FCTC WHO, 2018).[3]

Canada, one of the World Bank high income countries had 45,500 deaths attributable to tobacco smoking in 2012.[4] It is estimated that the burden of tobacco use in Canada costs upwards of $16.2 billion CAD per year.[4] Indirect costs such as premature mortality, loss of earnings, and illness/comorbidities are estimated to account for approximately $9.2 billion CAD.[4] While direct healthcare costs related to tobacco use such as hospital care, prescription drugs and physician visits/services amount to $6.5 billion CAD.[4] Encouragingly, there has been an overall decreasing trend in tobacco use, though predicting the continuation of this trend may have been over-estimated as the most recent data from 2017 shows an increase in the prevalence of current (past 30-day) tobacco cigarette use from 13% in 2015 to 15% (4.6 million) in 2017 and a continued decreasing gap between male and female current smokers (Figure 1.4).[5]

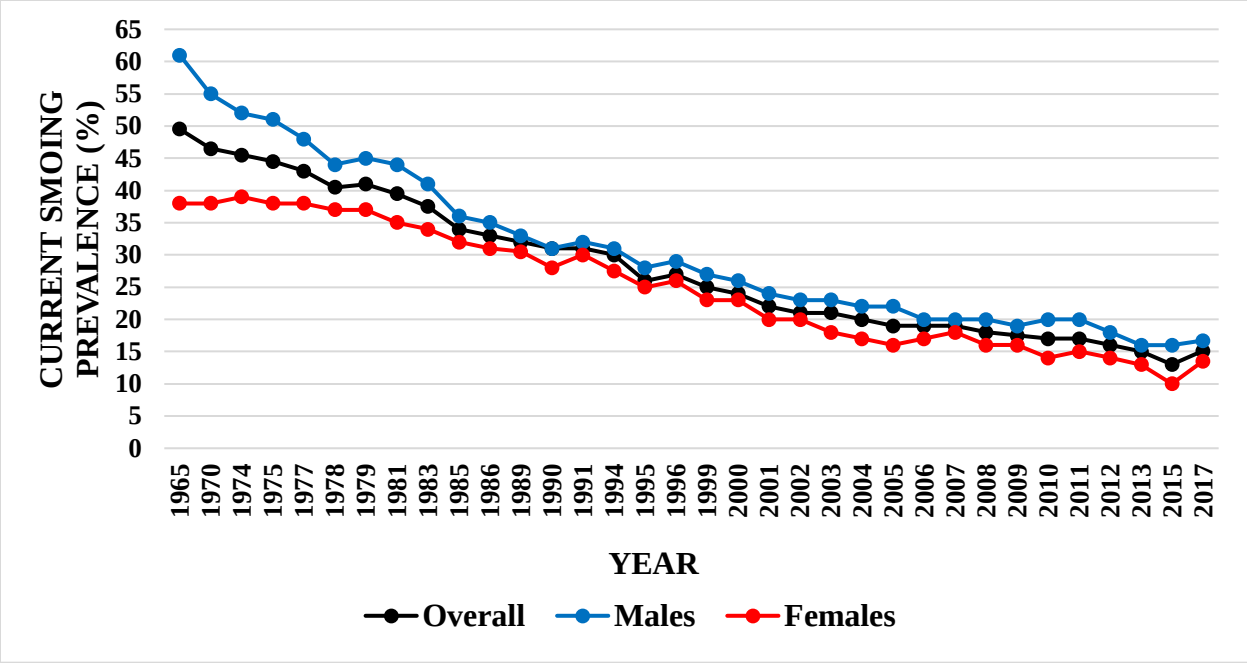

Figure 1.4: Trends in the prevalence of current (past 30-day) conventional tobacco smoking among Canadians aged 17 years and older from 1965-2017. Figure adapted from (Reid JL et. al, 2019).[5]

In order to remain profitable, the tobacco industry requires continued recruitment of new smokers to replace those that die prematurely (Figure 1.5). It is estimated that approximately 20% of all deaths in Canada per year are due to tobacco use[6] and the expected years of potential life lost (YPLL) due to tobacco smoke in Canada in 2002 was estimated to be 2,151 per 100,000 males (overall, not just smokers) and 1,302 per 100,000 females (overall, not just smokers) with an average age of death for males being 71.2 years and 73.4 years for females.[6]

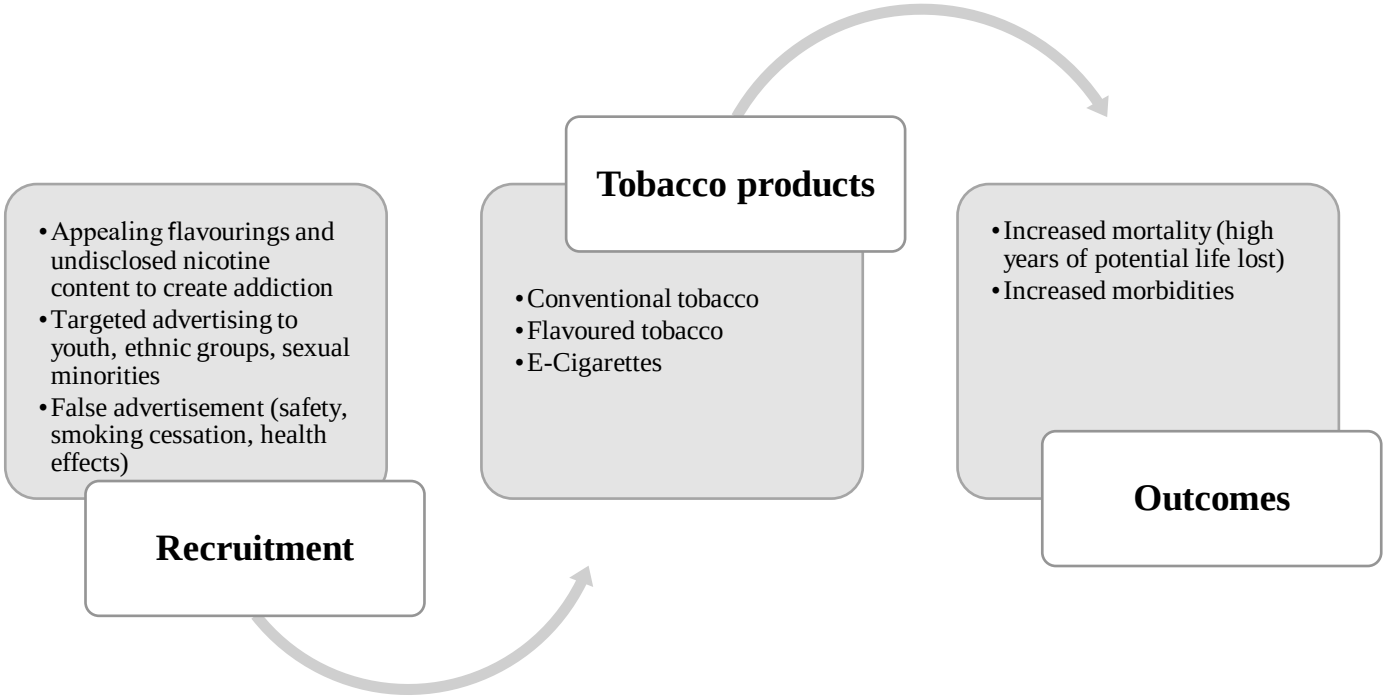

Figure 1.5: Tobacco industry growth relies on constant recruitment to replace lost consumers

Vulnerable populations are individuals or communities who due to disadvantage, inequity, social exclusion and social position are at increased risk of poor health.[7] A study conducted in 2013 using data about tobacco outlets from Ontario, Canada found that the majority of tobacco outlets were near schools and more likely to be in more deprived neighborhoods, increasing accessibility, normalization of the behaviour and susceptibility of youth and individuals with low socioeconomic status making them vulnerable to tobacco use.[8] Historically, the tobacco industry has targeted disadvantaged groups through marketing efforts which may have led to disparities in smoking status based on ethnicity, sexual orientation, age and social identity.[9] Documents revealed through litigation against the tobacco industry have shown the intentional targeting of youth through different methods to create a life-time consumer and to replace the tobacco smokers who die early.[10-12] Some of the methods used to attract vulnerable populations (e.g.

youth, sexual minorities) include targeted advertising,[11-14] appealing flavourings,[13,15,16] and false perceptions regarding the safety of the product including its role in smoking cessation.[15,17,18]

With new policies being implemented in Canada, there has been an overall decrease in conventional tobacco use; however, among users of non-cigarette tobacco products, 62% reported using a flavoured product, and among Canadian current (past 30-day) smokers, 9.3% reported smoking a menthol-flavoured cigarette over the past 30-days in 2017.[5] There has been a corresponding increase in electronic cigarette (e-cigarette) use, specifically experimentation (ever-use) and it is especially pronounced among Canadian youth (Figure 1.6).[5]

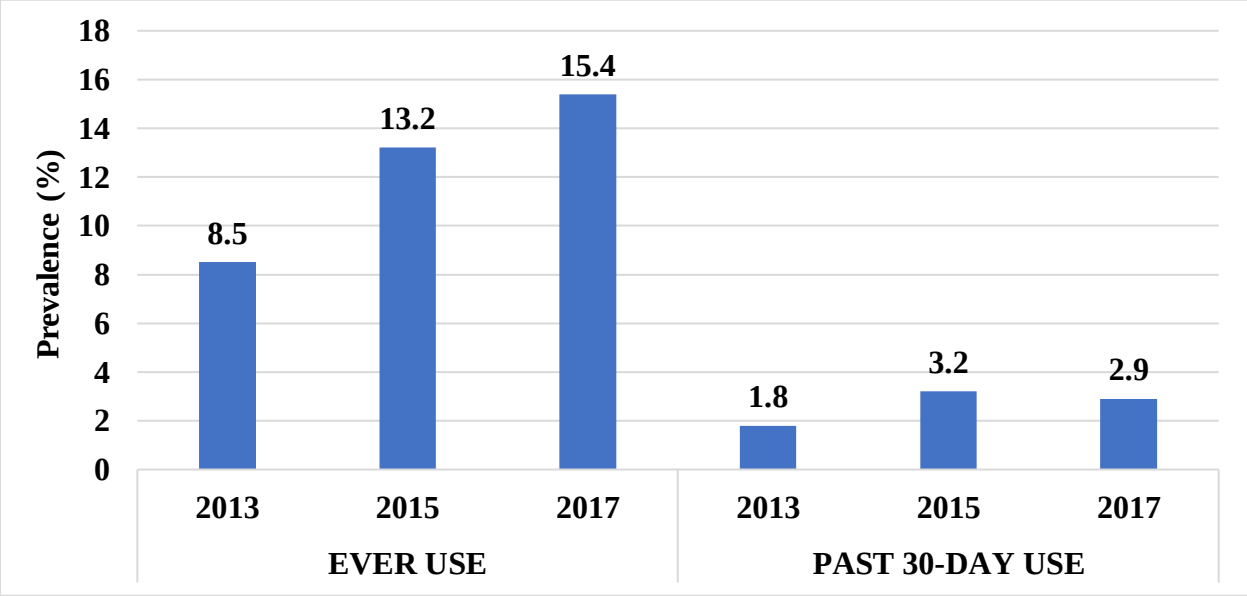

Figure 1.6: Prevalence of ever e-cigarette use and past 30-day e-cigarette use in Canada among adults 15 years or older 2013-2017. Figure adapted from (Reid JL et. al, 2019).[5]

To the best of our knowledge there have not been population based studies using Canadian data examining tobacco use among sexual minorities, who is at risk of flavoured tobacco use, what are the health effects of e-cigarettes and what is the relationship between e-cigarettes and conventional tobacco smoking. With the plethora of available nicotine delivery options in the market such as conventional tobacco cigarettes, flavoured tobacco cigarettes and electronic cigarettes, and with slowly evolving policies and restrictions, it is imperative to assess trends and determinants of their use. This is important as Canadian smoking related behaviours are continually evolving, with different sub-populations using different products (i.e. youth and young adults vs. older adults, by sex, and sexual orientation). Flavoured tobacco cigarettes were heavily marketed towards susceptible youth and more recently, e-cigarettes which are an electronic nicotine delivery system (ENDS) which has not been strongly regulated in Canada and thus may pose significant, previously uncharacterized/unknown health effects.

1.1.2 Flavoured tobacco smoking in Canada

Flavoured tobacco products (menthol cigarettes, flavoured little cigar or cigarillo, flavoured cigar, flavoured tobacco in water pipe [hookah]) come in flavours appealing to youth including vanilla, chocolate, bubble-gum, watermelon, cherry and strawberry.[19] They are packaged in attractive colours targeting youth and carried no health warnings.[19] Flavoured tobacco products are associated with less throat and upper respiratory tract irritation, making it easier to initiate tobacco use and to continue to smoke, exposing youth to the long term effects of nicotine and cigarettes.[19] This modality of tobacco exposure puts youth at risk to become addicted to nicotine and establish life-long patterns persisting into adulthood.[10]

Similar to current strategies being employed with e-cigarettes, flavoured tobacco products are falsely advertised as potential smoking cessation aids that led to harm reduction by the tobacco industry.[18] Moreover, similar to e-cigarettes today, most younger flavoured tobacco users believe them to be less harmful than regular cigarettes[20-22] with one third of US adults sampled in a study believing there were minimal harmful effects due to using flavoured tobacco products.[23] These inaccurate beliefs are based on effective and misleading marketing campaigns created by the tobacco industry[24] and oppose the increasing evidence detailing a plethora of negative health effects attributed to the use of flavoured tobacco.[25-27]

In 2010, due to the increased use of flavoured tobacco among Canadian youth,[28] and health concerns[29,30], federal legislation (Bill C-32)[31] was introduced to ban the sale of flavoured tobacco products (cigarettes, little cigars, cigarillos, and blunt wraps) weighing less than 1.4 g which contain flavouring agents excluding menthol which was argued to not be attractive to youth.[31] However, despite the introduction of legislation, over half of the tobacco using Canadian students reported using flavoured tobacco in 2011.[29] Contrary to suggestions that youth did not use menthol cigarettes, 32% of past 30-day tobacco users in Canadian high schools reported using menthol cigarettes in 2011.[29] Eventually, in 2018, amendments to the tobacco and vaping products act banned menthol and clove additives to all tobacco products.[32] Results of this policy change remain to be seen, but it could lead to a shift in Canadian smoking related behaviours from flavoured tobacco cigarettes to flavoured e-cigarettes, especially among youth.

1.1.3 Tobacco cigarette smoking among Canadian sexual minorities

Conventional tobacco cigarette use remains a significant public health concern among Canadians as the majority of Canadians who use nicotine products use conventional tobacco cigarettes. Therefore, the effects of policy and investigating smoking related behaviours among vulnerable subgroups is a necessity. Although extensive research on tobacco smoking behaviours and its prevalence already exists, there is limited research on the tobacco smoking behaviours of Canadian sexual minorities (lesbian, gay and bisexual). It has been estimated that 3.9% of Canadians are lesbian, gay or bisexual (LGB) according to the 2012 Canadian Community Health Survey – Mental Health (CCHS-MH).[33] Compounding the relationship between the LGB community (a highly vulnerable population) with tobacco cigarette use is that they have been historically selectively targeted and recruited by the tobacco industry[34-37] and report significantly higher risk for substance use including smoking, when compared to heterosexuals.[38-43]

Furthermore, sexual orientation has been reported to be independently related to many adverse health behaviours such as smoking, due to the unique risk factors faced by individuals who are identify as members of a sexual minority. The disparities reported in LGB smoking rates may be partially attributed to issues of disclosure, stigma and internalized homophobia.[44] Studies have suggested that sexual minorities experience disproportionately increased stress, depression, victimization, socialization in smoky areas, aggressive tobacco marketing, and substance abuse.[44-46] Moreover, minority stress theory posits that LGB individuals may use maladaptive coping behaviors, such as smoking because of their lived experience, facing chronic, social and structural stressors, which may partially help explain the higher rates of smoking seen in this unique population.[47-49] To date, the majority of studies investigating conventional tobacco smoking among Canadian sexual minorities have found increased rates of smoking, but these studies were limited by factors such as small sample sizes, limitations by biological sex (i.e. women only), evaluation of single groups (i.e. high school students, men who have sex with men) and geographical region, and to date there has not been a national study.[38-41]

1.1.4 Electronic cigarette use in Canada

E-cigarettes are a type of electronic nicotine delivery system (ENDS) containing batteries and emit vapour, however, no combustion takes place.[50] E-cigarettes contain a lithium battery, have a tank that is filled with e-cigarette liquid, an atomizer to heat the liquid and a mouthpiece for suction (Figure 1.7).[51]

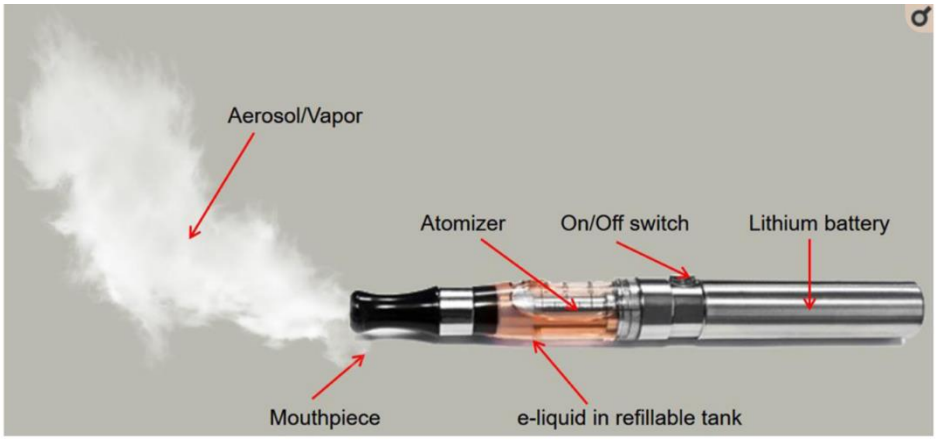

Figure 1.7: Schematic representation of an e-cigarette.[51] "Reprinted from Toxicology, Vol 365, Kaisar MA, Prasad S, Liles T, Cucullo L. A decade of e-cigarettes: Limited research & unresolved safety concerns, Page 68, Copyright (2016), with permission from Elsevier"

There are different levels of nicotine (from no nicotine to higher levels), and flavourings available which may appeal to youth and young adults similar to how flavoured tobacco was marketed.[52,53] Furthermore, there is evidence suggesting adult e-cigarette users are more likely to use tobacco flavour while youth were more susceptible to multiple flavour categories, the most common being fruit and candy[54] suggesting age based flavour preferences. This is unsurprising as flavoured tobacco is more attractive to youth rather than older adults;[55] and the longitudinal Population Assessment of Tobacco and Health Study in the USA found that youth who self-reported experimenting with tobacco products (cigarettes, flavoured tobacco, e-cigarettes, any cigar, hookah, smokeless tobacco, snus pouch, pipe, bidi, kretek, and dissolvable tobacco product use) consistently initiated with flavoured products.[56]

E-Cigarettes were patented globally by a Chinese pharmacist in 2007 and has since been adopted throughout the world.[51] The high rate of adoption globally can be attributed to several factors related to perceptions in safety, facilitating smoking cessation, low potential for harm, low price, lax policies, social trends and peer pressure.[51,57] E-Cigarettes are widely promoted on social media and misinformed beliefs and perceived knowledge are influencing e-cigarette use. A recent study concluded there are both negative and positive connotations regarding e-cigarette use on social media however, there were overall more positive sentiments,[58] with another study finding e-cigarette exposure through social media was associated with use through positive outcome expectancies in smoking experiences and sensory experience.[59] As social media is largely unregulated it is important for public health professionals to start disseminating evidence-based/science-supported information to impressionable youth on these platforms.

When examining the growth of e-cigarettes, a recent study from the United States concluded that nicotine containing e-cigarette use has nearly doubled among high school seniors from 11% to 21% over one year (2017-2018).[60] While in Canada, trends in e-cigarette use among youth have not been as pronounced, with 10% of Canadian students in grades 7-12 reporting past 30-day e-cigarette use (2016-2017), however, this is still an alarming trend as the rate has increased from 6.5% (2014-2015) according to the 2016-2017 Canadian Student Tobacco, Alcohol and Drugs Survey (CSTADS).[61] Interestingly, there has been substantial provincial variability in past-30 day e-cigarette use with students in Ontario reporting the lowest rate (6.6% in 2016-2017)[62] while Newfoundland and Labrador reported the highest rate of 22.4%,[63] higher than rates reported in the United States among high school seniors. When examining the overall rates of e-cigarette use in Canada, 1% (292,000) reported daily use, 2.9% (863,000) reported past 30-day use and 15.4% (4,600,000) reported being ever users (individuals who ever used an e-cigarette, even a few puffs) (Figure 1.6)[5] with males having a higher prevalence of ever use and past 30-day use consistently compared to females, and while the gap by sex has widened from 2013 and 2017, ever use of e-cigarettes continues to grow irrespective of sex (Figure 1.8).[5]

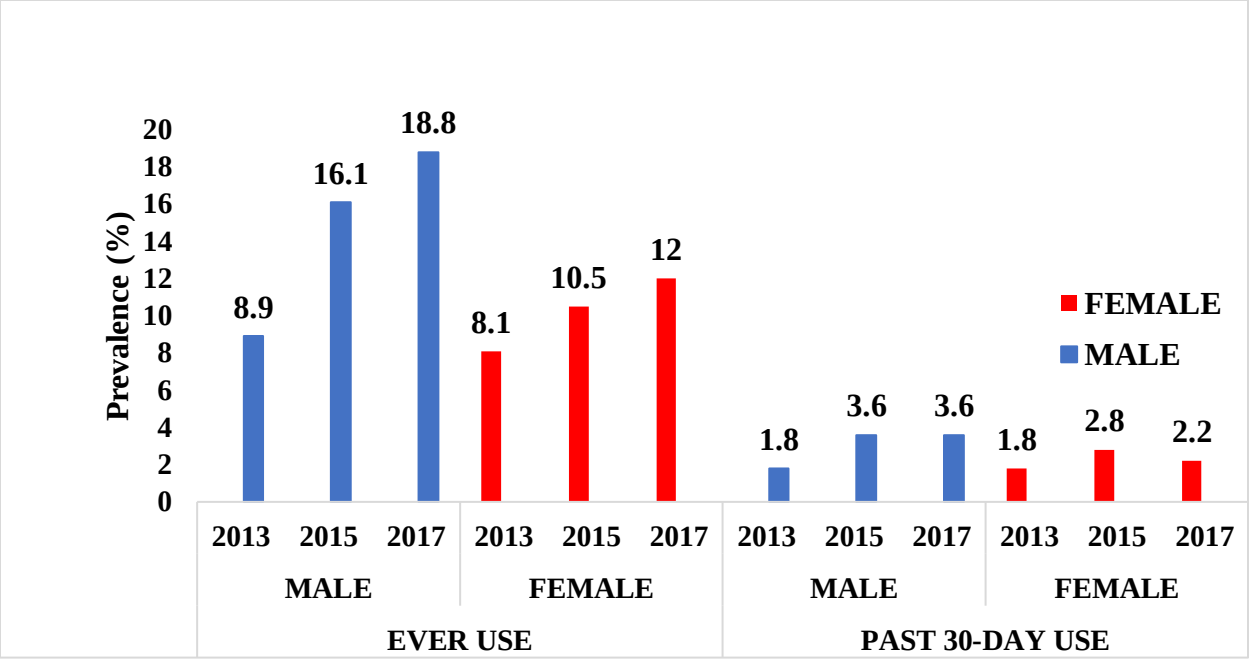

Figure 1.8: Prevalence of ever and past 30-day e-cigarette use among Canadian adults 15 years or older by sex, 2013-2017. Figure adapted from (Reid JL et. al, 2019).[5]

Studies examining the harm potential of e-cigarettes have found that they may actually be more addictive than conventional tobacco cigarettes,[64] and might be independently associated with a wide array of negative health consequences such as poor oral health,[65,66] asthma,[67] initiation of substance use and effects on brain maturation,[68] fetal development,[69,70] and chronic obstructive pulmonary disease (COPD).[71-74] In addition, there have been recently reported unexpected deaths linked to E-cigarette or Vaping-product associated lung injury (EVALI)[75,76] and injuries due to malfunction and or explosion of the device.[77,78]

1.1.4.1 Electronic cigarettes and chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease has a global prevalence of 65 million, and it is predicted to become the third leading cause of death worldwide by 2030.[79] Tobacco smoke has been identified as the dominant cause of COPD.[2] Thus, it is imperative to examine the effects of new nicotine delivery devices such as e-cigarettes in order to assess and characterize potential negative health outcomes associated with their use, such as COPD. A recent study has characterized the development of COPD like effects in mice inhaling nicotine containing e-

cigarette vapour by affecting cytokine expression, hyper-reactivity of the airway, and lung tissue destruction.[71] While an in-vitro study, examining the effect of e-cigarette vapour condensate on human alveolar macrophages concluded that there was evidence of up-regulation of oxidative stress related proteins such as MMP-9, reactive oxygen species, inflammatory cytokines and chemokines along with decreased bacterial clearance which enhances susceptibility to COPD.[72] Moreover, another *in vitro* study concluded that e-cigarettes had a lower impact on gene expression compared to conventional tobacco however an effect greater than standard air was seen in changes to genes mapping metabolic/biosynthetic processes, cell apoptosis, hypoxia and extracellular membrane pathways.[73] In addition, there is strong evidence indicating that the exposure to e-cigarette vapours impact airway inflammation, potentially via altering gene transcription and increase susceptibility to airway infection, the development of COPD, or even potentially lung cancer.[72-74] Conducting a population-based study using Canadian data to examine if an association exists between e-cigarette use and COPD using a large sample size, would add to the existing body of literature.

1.1.4.2 Electronic cigarettes and tobacco initiation

In Canada, two recently published longitudinal studies suggest that e-cigarettes are associated with conventional tobacco initiation.[80,81] This trend has been seen in other countries including the USA, Germany, UK and China (Taiwan). The growing evidence suggests e-cigarettes are potentially expanding the population of future conventional smokers as e-cigarettes are particularly attractive and addictive for never tobacco smokers (Figure 1.9).[81,82]

Figure 1.9: Paradigm shift in recruiting conventional tobacco users with potentially delayed effects seen at the population level

Based on these findings, it is entirely possible that e-cigarettes are a tool being used to circumvent policies enacted to combat the tobacco epidemic[3] and without appropriate safeguards in place (i.e. policy), there could be delayed long term adverse effects due to e-cigarette use unraveling the positive work done through health promotion, education and policy initiatives.

Insofar as current evidence, a recent systematic review and meta-analyses supports this hypothesis, finding that baseline ever e-cigarette users had a 30.4% pooled probability of tobacco initiation, while the probability of baseline never e-cigarette users initiating tobacco use was only 7.9% (an almost 8 fold increase), however there were limitations in the studies pooled.[83] In contrast, a 2019 study conducted in the US reported an association between the decrease in youth tobacco use with increased e-cigarette use but found no significant relationship between e-cigarette use and tobacco initiation; it is important to note that this study focused on youth and had a relatively short follow-up period potentially limiting the results.[84] As there is conflicting evidence in the literature with respect to the role of e-cigarettes in the conventional tobacco initiation, further examination is required with factors such as length of follow up, age, sex and magnitude of e-cigarette use (past 30-day/ever user/never user; acute vs. chronic user) needing to be standardized and accounted for.

1.2 Research Questions

This thesis aims to examine Canadian smoking related behaviours and to determine what are their prevalence, characteristics, determinants and health outcomes at the overall population level and stratified by vulnerable populations (LGB, high school students).

1.3 Objectives

To answer our research question, this thesis consists in four objectives:

To assess determinants of flavoured tobacco use among Canadian youth by analyzing a national generalizable survey (Chapter 3). This manuscript has been peer-reviewed and published.

To assess and determine the prevalence and determinants associated with tobacco cigarette use among the Canadian LGB community using national, generalizable data (Chapter 4). This article has been submitted for publication and currently under review.

To assess the prevalence of COPD among past 30-day e-cigarette users and to quantify the association between e-cigarette use and COPD as well as between dual use of tobacco and e-cigarettes, and COPD using Canadian data (Chapter 5).

To determine and quantify whether the use of e-cigarettes leads to conventional tobacco initiation among never users, a systematic review and meta-analysis (Chapter 6).

1.4 Relevance

In 2015, the Canadian Tobacco, Alcohol and Drugs Survey (CTADS) found the prevalence of current tobacco use (past 30-day) was the lowest ever recorded for Canadians (13%),[85] suggesting that health promotion, policy and anti-tobacco campaigns were delivering promising results. However, the 2017 CTADS found an increase in the prevalence of current (past 30-day) tobacco use of approximately 15%,[5] suggesting either a plateau in the efficacy of current efforts in curbing tobacco use or an actual unexpected increase due to novel trends/factors previously unaccounted for. An actual increase will lead to increased burden on the Canadian healthcare system and the population as a whole. As the Canadian population is steadily aging, significant increases in morbidity and mortality could have unforeseen impacts on the healthcare system. A recent review examining pro-tobacco and anti-tobacco campaigns aimed at vulnerable populations identified significant gaps in the literature pertaining to tobacco use among the lesbian, gay, bisexual and transgender (LGBT) population,[86] suggesting a need for additional studies. This is even further compounded in Canada as there is a major dearth in studies examining tobacco use patterns among the LGB community partially attributed to the small size of the community, requiring large sample sizes to make meaningful conclusions.[87] One of the objectives of this thesis is to assess trends and determinants of tobacco use among the Canadian LGB community, and to address the challenge of the sample size of the LGB population, several cycles of the Canadian Community Health Survey (CCHS) were merged and analyzed as indicated.

Although most of the flavoured tobacco has been banned in Canada since 2018, there are many lessons and relevant findings still applicable today. At the time of the study (Chapter 3), flavoured tobacco was not banned, and the use was still growing. Furthermore, it appears marketing strategies for flavoured tobacco have shifted to current e-cigarette marketing techniques. Flavoured tobacco was marketed as safe to use, with a low harm potential, less irritative to the throat and airway, with attractive flavours which appeal to youth, and as a potential tobacco cessation method.[18, 20-22] The flavoured tobacco products still available today in Canada including Hookah (Water Pipe) need to be followed. This study (Chapter 3) shed light on the prevalence and determinants of flavoured tobacco use among Canadian youth and results can be applied to e-cigarette use as well as to other forms of flavoured tobacco still available.

The Canadian Public Health Association (CPHA) released a statement in 2018 that stated the long term health effects of e-cigarettes are unknown, requiring further research and there is conflicting evidence on vaping devices acting as gateway devices to future conventional tobacco initiation.[88] There have been a significant amount of studies published since 2018 on e-cigarettes as a tobacco initiation devices warranting an updated systematic review and meta-analysis. This thesis aims to provide additional evidence from a Canadian perspective into potential harms of e-cigarettes, focusing on COPD and dual use of conventional tobacco products with e-cigarettes. Our results will help assess whether e-cigarettes are potentially harmful by assessing the association between COPD and e-cigarettes and if they may serve as tobacco initiation devices.

By applying the multiple tobacco product use framework,[89] examining the relationship between Canadian smoking related behaviours (conventional tobacco, flavoured tobacco and e-cigarettes) and their determinants, prevalence in vulnerable populations and potential harms will be studied while accounting for person-level factors, situational factors, and product level factors.

The first two objectives focus on the prevalence, trends and determinants of tobacco use among vulnerable Canadian populations: Canadian high school students in grades 10-12 and the LGB population. The latter two objectives will examine e-cigarettes; specifically, whether their use is associated with COPD using a large dataset (data from Ontario, British Columbia, Nova Scotia and Northwest Territories) and whether they can cause tobacco initiation leading to unforeseen future adverse effects (Figure 1.10).

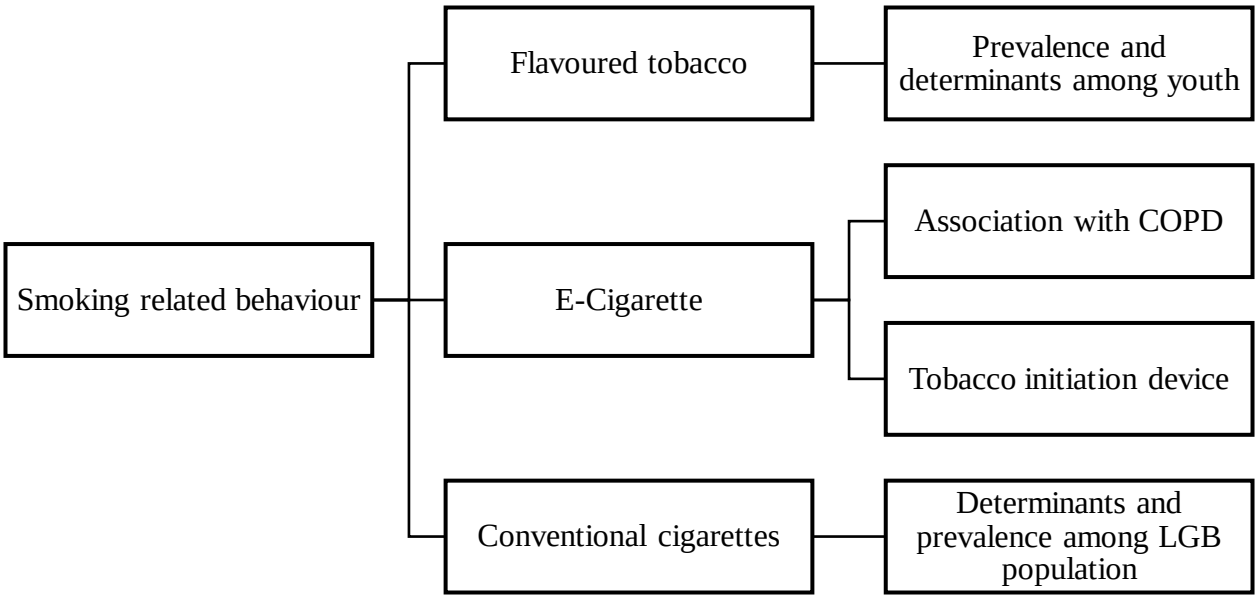

Figure 1.10: Overview of the objectives of this thesis

This thesis adds to tobacco-related research in Canada by, by addressing several gaps in current knowledge, provides new evidence, and results have been presented at different conferences in both oral and poster presentations. Four manuscripts have been prepared as follows.

1. To address the prevalence and determinants of flavoured tobacco use among Canadian youth, a potential conventional tobacco initiation gateway (Chapter 3).
2. To examine determinants and the prevalence of tobacco smoking among the Canadian LGB community using a population-based dataset (Chapter 4).
3. To examine if e-cigarette use is independently associated with COPD using Canadian data (Chapter 5).
4. To provide additional evidence to address the lack of consensus regarding the role of e-cigarettes as tobacco initiation devices by collating the latest results from ongoing longitudinal studies and incorporating them with previous data (Chapter 6).

Overall, this thesis provides up to date, new evidence about Canadian smoking related behaviours to better inform public health practitioners, patients, family members, and policy makers thus positively impacting health, awareness and tobacco control and prevention efforts at the individual and population level.

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CHAPTER 2: METHODS

2.1 Multiple tobacco product use theoretical framework

The multiple tobacco product use theoretical framework (MTPTF) draws from health behaviour theories, marketing and behavioural economic literatures.[1] When assessing determinants (Chapter 3, Chapter 4, Chapter 5), choosing what factor(s) to include in multivariable analysis requires statistical, temporal, social and biological considerations to be taken into account.[2] A conceptual framework allows the understanding of the hierarchical relationships between the variables, what their relationship is and help to organize potential research ideas but do not explain outcomes.[2,3] Theories are developed based on conceptual frameworks which help in elaborating hypotheses, assumptions and direction, after which models are developed to test the assumptions about the variables and outcomes under study.[3] Incorporating a conceptual framework, and theory allows for a logical model to be developed facilitating in identifying and testing relevant research questions. The variables tested in this paper (Chapter 3-5) were based on the MTPTF, and using this conceptual framework allowing us to understand the relationship between variables, followed by the development of our theory gives us a sound foundation and improves our final effect estimates.[2]

The MTPTF framework improves the understanding of the influence of one nicotine related product on others (i.e. e-cigarettes on conventional tobacco, flavoured tobacco on conventional tobacco etc.), understanding the proximal and distal determinants of specific smoking related behaviours (i.e. e-cigarettes *vs.* conventional tobacco *vs.* flavoured tobacco), and how they impact health (i.e. COPD).[1] Furthermore, this theoretical framework accounts for individual factors, the influence of the product on the individual and situational factors, and product characteristics, and how they impact smoking related behaviours (Figure 2.1).[1]

Therefore, for the purposes of this thesis, the MTPTF is an ideal framework to help identifies factors in a hierarchical manner that need to be assessed when examining the association between smoking related behaviours and negative health outcomes (COPD, tobacco initiation, flavoured tobacco use and standard tobacco use), accounts for vulnerable populations through "person x product" and person-level factors (i.e. LGB community, impressionable youth) and helps examine the interplay between choices made between different smoking related behaviours (i.e. dual e-cigarette and tobacco use). For the purposes of this thesis we will incorporate person-level, situational and product factors, examine the dynamic complementarity between e-cigarettes and conventional tobacco, examine the effects on health outcomes and addictive potential.

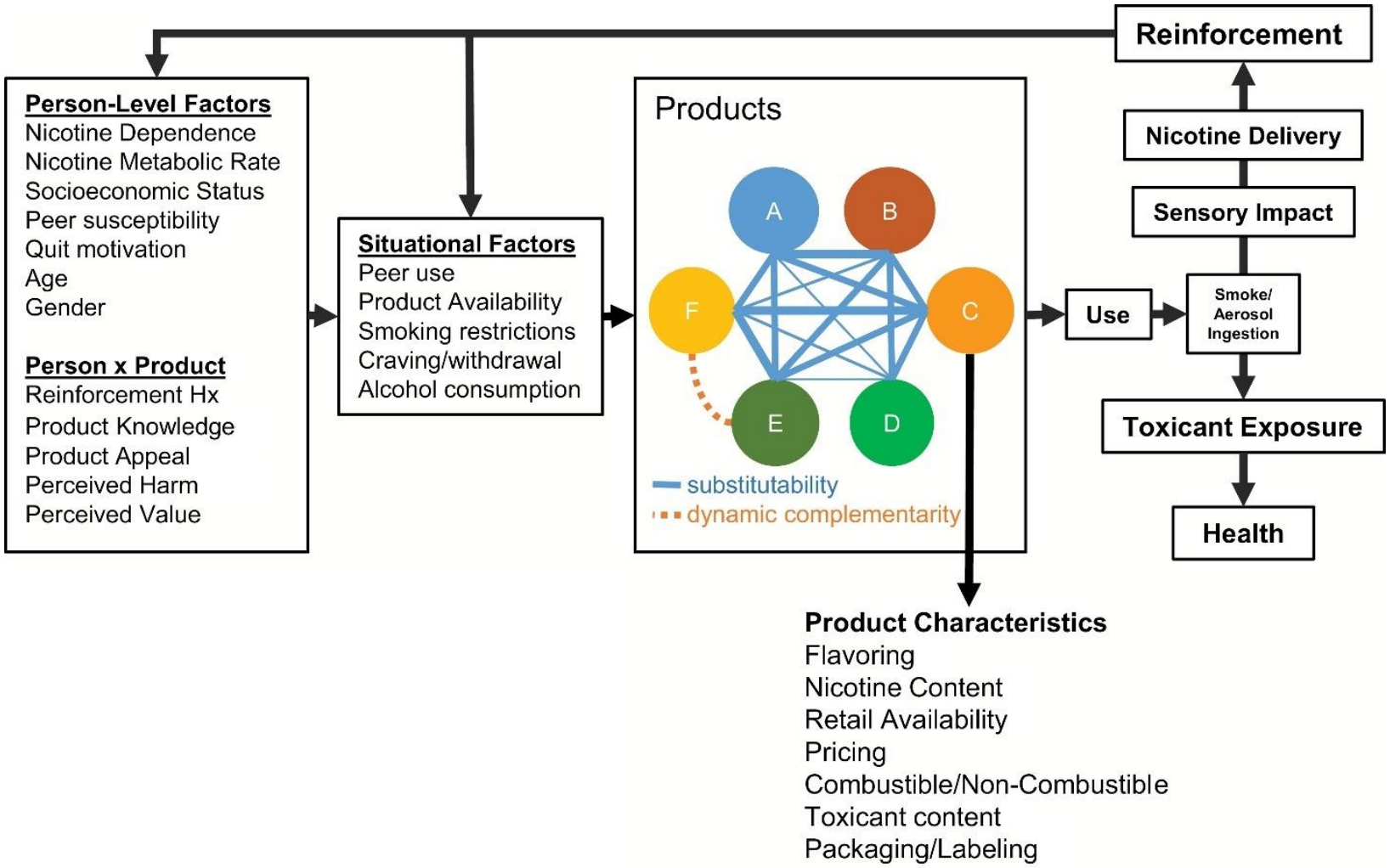

Figure 2.1: The multiple tobacco product use conceptual framework (Pacek LR, et al. 2019).[1] Figure modified with permission from Oxford University Press. *Hx denotes history*
Products A-F are different tobacco products such as conventional tobacco cigarettes, flavoured tobacco cigarettes and e-cigarettes

2.2 Study design

This thesis uses two types of study design, cross-sectional (Chapter 3, 4, 5), and a systematic review and meta-analysis (Chapter 6). The cross-sectional studies enable the analysis of large population cohorts and sub-populations in an comprehensive and timely manner.[4] They are of value for the purpose of this thesis because Canadian smoking related behaviours continue to develop and evolve, and otherwise it will take decades to assess the long-term consequences of newer tobacco/nicotine products (i.e. e-cigarettes). As such, cross-sectional studies are quick, usually covering one time point or a short time period. Results can estimate the prevalence of a given outcome (i.e. smoking behaviour), allowing for the assessment of current patterns (i.e. changes in tobacco use among Canadians).[5] Due to the recent emergence of alternative tobacco products (i.e. flavoured tobacco, e-cigarettes), cross-sectional studies are a valuable tool for public health planning, allowing for a early understanding of the etiology of the specific behaviour, and for hypothesis generation.[5] There are limitations when using cross-sectional studies; we cannot infer causation due to not having a temporality component, only the association between outcome and exposure, data is representative of a specific period of time and the potential for bias when assessing mortality as risk factors that result in death are under-represented in the diseased, especially in cases of chronic disease states.[5]

Systematic review and meta-analysis are useful to provide pooled information to address the current gaps in the knowledge.[6] For the purpose of this thesis, we will use a systematic review and meta-analysis to address an area with a lack of consensus in the literature, whether existing evidence supports the hypothesis that e-cigarettes are tobacco initiation devices. A systematic review uses explicit methodology to minimize bias when attempting to collect evidence based on pre-specified eligibility criteria.[6] There are four components to a proper systematic review: a. clear objectives with reproducible methodology; b. systematic search to include studies meeting the eligibility criteria; c. assessing the validity of the included studies and d. a systematic presentation of the characteristics, findings and synthesis of the included studies.[6,7] The meta-analysis allows the combination of data from different studies to provide a better estimate of the relationship between the intervention/exposure (i.e. e-cigarette use) and outcome (i.e. tobacco initiation).[6] Due to the recency of e-cigarette use, there are few longitudinal studies currently

available assessing their effect on conventional tobacco initiation and there are some conflicting findings. Using this approach allows us to account for disparities and studies heterogeneity in the literature, and to minimize bias by using a specific, reproducible, and rigorous methodology.[7]

2.3 Data sources

The Youth Smoking Survey (YSS) is a Canadian national cross-sectional, stratified design, school-based survey. The 2012-2013 cycle was used for analyzing the prevalence of flavoured tobacco use and assessing the risk profile of Canadian youth in Chapter 3. Data was collected from students in grades 7-12 across 450 schools in Canada. Schools from the province of Manitoba and the Northwest, Nunavut and Yukon territories and students living in institutions or on First Nations reserves did not participate in the survey.[8] Stratification was based on health region smoking rates, the participating school's postal code and the population size of major metropolitan areas.[8] The survey's design and sample weight allow for population-based estimates.[9]

To examine the association between sexual orientation and smoking preferences among LGB Canadians (Chapter 4), the Canadian Community Health Survey (CCHS) cycles from 2009-2014 were used. The CCHS is an annual, nationally representative, population-based survey, which aims to assess the health status, health service usage and determinants of health among people living in Canada.[10] Data analysis was conducted in the Saskatchewan Research Data Centre (SKY-RDC), and the CCHS master files from survey cycles (2009-2014) were merged and analyzed using a pooled approach to maximize the sample size due to the low prevalence of sexual minority respondents. Merging the cycles and scaling of the weights were conducted according to established guidelines.[11] Due to privacy concerns, the RDC only released weighted results to be generalizable to the Canadian population aged 18-59 years old.

The CCHS 2015/2016 cycle (same survey design as Chapter 4 but different cycle) was used to assess the prevalence of COPD among e-cigarette users in Ontario, British Columbia, Nova Scotia and the Northwest Territories, to determine whether an association between e-cigarette use and chronic obstructive pulmonary disease (COPD) exists and what is the effect of dual use (e-cigarette and conventional tobacco) on the association with COPD in Chapter 5. The final

sample size in this analysis was 37.754 individuals aged 35 years or older, with the prevalence of COPD being 5.35% and the prevalence of past 30-day e-cigarette use being 2.31%.

For the systematic review and meta-analysis examining whether e-cigarettes are tobacco initiation devices (Chapter 6), the following databases were searched: PubMed, MEDLINE: Ovid MEDLINE, Public Health Database, Scopus and Cochrane Library databases. Longitudinal studies published since 2010 were included. The PRISMA-P guidelines were followed in the conception, methodology and reporting of this systematic review and meta-analysis.[6]

2.4 Sex and gender in health research

In chapters 3-5, sex and gender, important health determinants are incorporated in our analysis where applicable. By including sex and gender in research, their health impacts can be assessed, and innovative evidence can be used to improve the health of everyone.[12] Sex and gender are often overlooked but important factors to improve the external validity of research in order to make the results generalizable to the entire population.[13] Failure to account for these factors in research could potentially lead to greater health inequities.[14]

The Canadian Institutes of Health Research (CIHR) defines sex as "a set of biological attributes in humans and animals. It is primarily associated with physical and physiological features including chromosomes, gene expression, hormone levels and function, and reproductive/sexual anatomy. Sex is usually categorized as female or male but there is variation in the biological attributes that comprise sex and how those attributes are expressed."[15] Gender on the other hand is defined as the "socially constructed roles, behaviours, expressions and identities of girls, women, boys, men, and gender diverse people. It influences how people perceive themselves and each other, how they act and interact, and the distribution of power and resources in society. Gender is usually conceptualized as a binary (girl/woman and boy/man) yet there is considerable diversity in how individuals and groups understand, experience, and express it."[15]

In chapters 3 and 5 we used biological sex to assess sex-based differences in the determinants flavoured tobacco use (Chapter 3) and to assess the association between e-cigarette use and chronic obstructive pulmonary disease (Chapter 5). In Chapter 4 we examine whether sexual orientation is independently associated with conventional tobacco smoking. Here, we examine biological sex and sexual orientation. While sexual orientation is distinct from gender, there is an

intersection between the two among communities who do not identify as heterosexual or cis-gender.[16] For the purpose of the study in chapter 4, we used the definitions for sexual orientation as stated by the CCHS; heterosexuals are individuals that have sexual relations with people of the opposite sex, gay are biological males that have sexual relations with biological males, lesbian are biological females that have sexual relations with biological females and bisexual are individuals that have sexual relations with both sexes.[17] By examining both biological sex and sexual orientation and disaggregating the data by biological sex we were able to better account for these health determinants and improve the external validity of our results.

2.5 Regression analysis

2.5.1 Logistic regression

Logistic regression is a versatile regression technique that can be used to measure the association between an exposure and outcome, predict outcomes and control for confounding.[18-20] Logistic regression can be utilized for binary outcome events (i.e. flavoured tobacco use, Chapter 3; and past 30-day e-cigarette use, Chapter 5) with either continuous, ordinal or categorical independent variables.[18] By incorporating multiple variables we get a better estimate of the pure effect of the independent variable of interest when adjusting for the other independent variables.[18] Assumptions for logistic regression include the independence of observations, linear relationship between logit for continuous variables and the logit of the outcome variable, no multicollinearity between the independent variables and no highly influential outliers.[18]

Variable selection in this thesis were based on variables included in the multiple tobacco product use framework (Figure 2.1), clinical considerations, and literature review. To build our models in Chapters 3,4,5 we used the purposeful selection methodology.[18-20] The purpose of this methodology is to develop the most parsimonious model that best represents the outcomes of the data.[19] After assessing descriptive statistics between the outcome and independent variables, univariate analysis was conducted in order to determine the crude (unadjusted) association between the outcome variable and each independent variable using a p-value of 0.25.[19] Variables found statistically significant in univariate analysis were kept for multivariable model building. When building the multivariable models, we used backwards elimination strategy where all significant independent variables were initially included. Variables that were not statistically or clinically significant (p-value > 0.05) were removed one at a time. When a variable was

removed, the regression coefficient (β) of the primary independent variable (i.e. e-cigarette use in chapter 5) was compared in the initial model and the new model without the variable that was removed. If the difference in the regression coefficient was greater than 20%, the variable removed was providing an important adjustment and returned and kept in the model.[19] Once model fit is complete, multicollinearity is assessed via the variance inflation factor (VIF) and tolerance (TOL) values. If VIF ≥ 2.5 we assumed there is evidence of multicollinearity.[21] All two-way interactions were assessed between the primary independent variable and other independent variables. In Chapter 5, we have evidence of effect modification by sex which was included in Models 2 & 3. Once the final model is complete, model fit was assessed using the Hosmer Lemeshow Goodness of Fit test where a non-significant value (p-value > 0.05) suggests the model is a good fit of the data.[19] In cases where we had to select between statistically similar models, we used the simpler, more parsimonious model unless relevant practical/clinical considerations were lost by dropping variable(s) of interest. Odds ratios were reported, which give the strength of association between the independent variable and the outcome after controlling for the other independent variables.[18]

2.5.2 Multinomial logistic regression

Multinomial logistic regression is similar to binary logistic regression however the outcome variable has greater than two levels.[22,23] In Chapter 4 we use a multinomial logistic regression with conventional tobacco use status (nominal categories: current user, former user and never user) being the levels of the outcome variable. Model building followed the same steps as with binary logistic regression analysis however the deviance was used as the Goodness of Fit test with a deviance > 0.05 indicating the model adequately fits the data.[22] The outcome will be an odds ratio but with each level compared to the reference group. For example, in Chapter 4 we can see the odds ratio were interpreted as current smoker *vs.* never smoker and former smoker *vs.* never smoker.

2.6 Systematic Review and Meta-Analysis

The systematic review and meta-analysis conducted in Chapter 6 follows PRISMA-P guidelines.[6] The population of interest are humans who are never tobacco smokers at baseline. The intervention of interest is e-cigarette use, comparators are never e-cigarette users and the outcome of interest is tobacco initiation and current conventional tobacco use. Methods are discussed in detail in Chapter 6. The risk of bias is assessed using a modified Newcastle Ottawa Scale for cohort studies.[24] The meta-analysis was conducted using Comprehensive Meta-Analysis version 3 (Biostat Inc., Englewood, NJ, USA).

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CHAPTER 3: PREVALENCE AND CHARACTERISTICS OF FLAVOURED TOBACCO USE AMONG STUDENTS IN GRADES 10 THROUGH 12: A NATIONAL CROSS-SECTIONAL STUDY IN CANADA, 2012-2013[1]

Introduction: Tobacco use is the leading cause of preventable death in Canada and worldwide. Despite decreases in the prevalence of smoking in Canada, increases in flavoured tobacco use by youth poses a serious public health concern. This study examined the prevalence and characteristics of flavoured tobacco use among a national sample of students (grades 10-12).

Methods: This study used a cross-sectional design on a nationally generalizable, school-based, Youth Smoking Survey (YSS), 2012–2013. It incorporated data from a representative sample of 19,979 students in grades 10–12 from across Canada. Univariate and multivariate logistic regression models were used to examine differences in flavoured tobacco use by demographic and social characteristics.

Results: This study found that 14.8% of the participating students used flavoured tobacco in the past 30-days. Results of the logistic regression analysis show that flavoured tobacco use was significantly higher among male students [(aOR = 1.63; 95% CI = 1.36–1.95)], who had at least one friend or sibling who smoke [(aOR = 2.20; CI = 1.62 to 2.99) and (aOR = 1.51; CI = 1.22 to 1.88), respectively] and who received greater than $20/week in personal spending money [(aOR = 1.76; CI = 1.26 to 2.45)].

Conclusions: The results of our study indicate that flavoured tobacco use is a public health concern and has a strong appeal among youth in Canada. This is a particularly troubling finding, especially in light of the fact that there is a national ban on certain flavoured tobacco products. To be effective, strategies specifically tailored for youth using flavoured tobacco would require appropriate educational/prevention initiatives, more comprehensive legislation and better regulatory mechanisms.

Keywords: Flavoured tobacco, Adolescents, Canada

[1] Bird Y, May J, Nwankwo C, **Mahmood R**, Moraros J. Prevalence and characteristics of flavoured tobacco use among students in grades 10 through 12: a national cross-sectional study in Canada, 2012–2013. Tobacco induced diseases. 2017 Dec 1;15(1):20.

3.1 Introduction

Tobacco use is the leading cause of preventable death in Canada and the world.[1] It has been associated with a range of medical conditions known to cause significant morbidity and mortality.[1] Current global estimates of the mortality from tobacco stand at 6 million deaths annually.[2] Since the 1990's, intense public health efforts have concentrated in reducing the burden of disease resulting from tobacco. These actions have effectively contributed to a steady decline of smoking rates over time.[3,4] In Canada, it is estimated that the prevalence of smoking is currently at its lowest point in nearly two decades[4] and the average number of cigarettes smoked daily has decreased by more than 2 cigarettes since 1999.[3]

These encouraging trends are threatened by the documented growing appeal of flavoured tobacco (menthol cigarettes, flavoured little cigar or cigarillo, flavoured cigar, flavoured tobacco in water pipe [hookah]) among youth.[5,6] It has been reported that approximately 2 of every 5 current youth smokers (approximately 126,000 young Canadians), use flavoured tobacco.[7] These tobacco products come in flavours that appeal to youth including vanilla, chocolate, bubble-gum, watermelon, cherry, and strawberry. They are packaged in enticing colours aimed at youth and carry no health warnings. They are associated with less throat and upper respiratory tract irritation, which makes it easier to start and continue to smoke them and exposes youth to the long-term effects of nicotine.[8] This puts youth at risk to become addicted and establish use patterns/addiction that persist into adulthood, making them life-long tobacco consumers.[9]

Flavoured tobacco products have been falsely advertised as possible aids for smoking cessation and harm reduction by the tobacco industry.[10] Thus, it is not surprising to find that most young flavoured tobacco users believe them to be less harmful than regular cigarettes.[11-13] Similarly, one third of adults sampled in a US study believed the harmful effects of flavoured tobacco to be minimal.[14] These erroneous beliefs are fundamentally premised on an effective but misleading marketing campaign by the tobacco industry[15] and stand in stark contrast to the mounting evidence in the literature that details a number of deleterious effects attributed to the use of flavoured tobacco.[16-18]

In Canada, concerns over the health effects of flavoured tobacco products[5,19] along with their rise in popularity among youth[20] led the Canadian government to implement Bill C-32 in July 2010.[21] Bill C-32 prohibits the sale of cigarettes, little cigars and cigarillos, and blunt wraps that weigh less than 1.4 g and contain flavouring agents (excluding menthol). However, Bill C-32 does not cover all tobacco products and many manufacturers simply increased the weight of their products to more than 1.4 g to circumvent the law. Thus, despite the national ban, it has been reported that more than half of high school students in Canada who smoke, use flavoured tobacco.[6]

Flavoured tobacco use among Canadian youth is the result of a set of complex and dynamic interactions between youth and their social environment. However, the interactions between their demographic (sex, grade and ethnicity) and social characteristics (friends, siblings, parents/guardian who are smokers and weekly personal spending money) have not been sufficiently studied. The present study aims to use a large, nationally representative sample in order to identify the prevalence and characteristics associated with the use of flavoured tobacco among Canadian students in grades 10 through 12.

3.2 Methods

3.2.1 Study design

This study used a cross-sectional, stratified design on a nationally generalizable, school-based Youth Smoking Survey (YSS) in 2012–2013. Stratification was based on the health region smoking rates (as determined by the Canadian Community Health Survey data), the participating school's postal code and the population size of major metropolitan areas.[22] The survey design and sample weights allow for population-based estimates and have been explained in detail elsewhere.[23]

3.2.2 Participants

The 2012–2013 YSS involved a total of 38,667 student participants from grades 7–12 across 450 schools in Canada. Schools from the province of Manitoba and the Northwest, Nunavut and Yukon territories as well as students living in institutions or on First Nations reserves did not participate in the survey. Research has shown that students in lower grades (7–9) differ significantly from students in higher grades (10–12) with regard to their behaviours and a variety of measures relating to tobacco use.[24] Our study focused on students in grades 10–12 (n = 19,979).

3.2.3 Variables explored

Outcome variable

The outcome variable was current flavoured tobacco use (past 30-day use). The outcome variable was derived from a question in the YSS asking: "In the last 30-days, did you use any of the following flavoured tobacco products?" Responses included: "menthol cigarettes (Yes/No), flavoured little cigar or cigarillo (Yes/No), flavoured cigar (Yes/No), flavoured tobacco in water pipe (hookah) (Yes/No)." Students who answered yes to any of these four questions were classified as being current flavoured tobacco users.

Independent variables

The independent variables of interest included the respondent's demographic (sex = male/female; ethnicity = White, Black, Asian, Aboriginal, Hispanic; grade = 10–12) and social characteristics (how many of the respondent's friends, siblings and parents/guardians are smokers = 0, 1, 2, 3 or more; weekly personal spending money = $0 to > $100).

3.2.4 Data analysis

The survey was weighted by the data provider in order to adjust for differential response rates across groups and to allow for generalization of the findings to the Canadian student population.[22] Our study used descriptive analysis to summarize the basic features of the data, looking at frequencies and distributions of the outcome and independent variables of interest. Univariate analysis was conducted to determine the crude association between each of the independent variables (sex, grade, ethnicity, number of friends, siblings, and parents/guardians who smoke and weekly personal spending money) and the outcome variable of interest (flavoured tobacco use). Logistic regression modelling was carried out using the PROC SURVEYLOGISTIC command to examine the relationship between flavoured tobacco use and the independent variables of interest.

Assumptions of logistic regression were checked, and backwards elimination strategy was used, when developing the models. When variables were removed, confounding was assessed at each stage. If there was a change in the effect estimate of the primary independent variable by 20% or more with the inclusion of a variable, the variable would be retained in the model as a confounder. All possible two-way interactions involving the primary independent variable and the variables of interest were assessed using a p-value of 0.05 for statistical significance. All analysis was carried out using SAS version 9.3.

3.3 Results

3.3.1 Descriptive statistics

In 2012–2013, 14.8% of the participating students from grades 10–12, self-identified as having used flavoured tobacco over the past 30-days in Canada. Past 30-day use of flavoured tobacco as a percentage was highest among males (18.8%), who attended 12th grade (17.4%), and who self-reported being Aboriginal (23.9%), Hispanic (21.3%) and Black (19.0%). Also, youth who used flavoured tobacco products in the past 30-days, reported having one or more friends who smoked (68.3%), one or more siblings who smoked (91.2%), and one or more parents/guardians who smoked (63.9%). In terms of their weekly personal spending, 23.3% reported having greater than $100 per week to spend on themselves, while 8.7% reported having no personal weekly monies (Table 3.1).

Table 3.1: Descriptive characteristics of the study population among 10–12 grade school students in Canada, 2012–2013

Variables		Flavoured Tobacco Use (Past 30 days)	No Flavoured Tobacco Use (Past 30 days)	Total (N)
Outcome Variable				
Flavoured Tobacco Use (Past 30-days)		14.77%	85.23%	19979
Independent Variables				
Sex (n=19979)	Female	10.9%	89.1%	10171
	Male	18.8%	81.2%	9808
Grade (n=19979)	10	12.7%	87.3%	7544
	11	15.0%	85.0%	6982
	12	17.4%	82.6%	5453
Ethnicity (n=18818)	White	14.5%	85.5%	14389
	Black	19.0%	81.0%	814
	Asian	7.5%	92.5%	1942
	Aboriginal	23.9%	76.1%	1270
	Latin American/ Hispanic	21.3%	78.7%	403
Friend Smokers (n=18048)	None	4.6%	95.5%	9861
	One	12.1%	87.9%	2278
	Two	19.7%	80.3%	1571
	Three or more	36.5%	63.5%	4338
Sibling Smokers (n=18141)	None	11.0%	89.0%	14149
	One	23.2%	76.8%	2763
	Two	25.9%	74.1%	718
	Three or more	42.1%	57.9%	511
Parent/Guardian Smokers (n=18921)	None	10.4%	89.6%	10935
	One	16.5%	83.5%	4284
	Two	20.1%	79.9%	2107
	Three or more	27.3%	72.7%	1595
Weekly Personal Spending (n=16546)	Zero	8.7%	91.3%	2783
	$1-$5	12.5%	87.5%	869
	$6-$10	10.3%	89.7%	1199
	$11-$20	12.6%	87.4%	2594
	$21-$40	17.1%	82.9%	2639
	$40-$100	16.7%	83.3%	2733
	>$100	23.3%	76.7%	3729
Self-Esteem (n=19923)	High	14.6%	85.4%	12485
	Intermediate	14.3%	85.7%	6667
	Low	21.9%	78.1%	771

3.3.2 Logistic regression analysis

Univariate analysis suggests that sex ($p < 0.0001$), grade ($p < 0.0003$), ethnicity ($p < 0.0001$), friends who smoke ($p < 0.0001$), siblings who smoke ($p < 0.0001$), parents/guardians who smoke ($p < 0.0001$) and weekly personal spending money ($p < 0.0001$) were significantly associated with flavoured tobacco use among students in grades 10–12. Odds ratios are shown in relation to a reference category for each variable (Table 3.2).

Multivariable logistic regression analysis examined the odds of being a flavoured tobacco user. Male students were aOR=1.63 (95% CI: 1.36-1.95) times more likely to be flavoured tobacco users compared to females when adjusting for ethnicity, friends who smoke, siblings who smoke and weekly personal spending. In our final model (adjusted for sex, ethnicity, friends who smoke, siblings who smoke and weekly personal spending), the variables of "friends who smoke" showed a graded association of a student using flavoured tobacco as the number of friends who smoke increased from one (aOR = 2.20, 95% CI: 1.62-2.99) to two friends (aOR = 3.80, 95% CI: 2.71-5.31) and three or more friends who smoke (aOR = 7.08, 95% CI: 5.66-8.86), when compared to students who reported having no friends who smoke. A similar pattern was seen with siblings who smoke, as individuals who had one sibling (aOR = 1.51, 95% CI: 1.22-1.88), two siblings (aOR = 1.55, 95% CI: 1.09-2.20) and three or more siblings who smoke (aOR = 3.40, 95% CI: 2.33-4.96) demonstrated a graded association with flavoured tobacco use, when compared to students with no siblings who smoke. When examining the association between weekly spending and flavoured tobacco use, individuals with the highest weekly spending (greater than $100 per week in personal spending) had the strongest association with flavoured tobacco use (aOR = 2.46, 95% CI: 1.82-3.33) compared to individuals with no weekly personal spending. There were no statistically significant associations with parent/guardian smokers or by high school grade (grade 10, 11, 12) and a student using flavoured tobacco (Table 3.3).

It is important to note that complete case data was used in this analysis which resulted in a sample size of 13,139 from the initial 19,979 respondents. As a result there is potential for biases in our estimates.

Table 3.2: Univariate analysis of flavoured tobacco use among 10–12 grade school students in Canada, 2012–2013

Variables		**Odds Ratio (95% CI: Lower to Upper)**	**p-value**
Sex (Ref=Female)	Males	1.73 (1.48-2.02)	< 0.0001
Grade (Ref=Grade 10)	Grade 11	1.20 (1.00-1.44)	0.0003
	Grade 12	1.53 (1.24-1.87)	
Ethnicity (Ref = White)	Black	0.83 (0.58-1.19)	< 0.0001
	Asian	0.53 (0.39-0.71)	
	Aboriginal	2.17 (1.74-2.70)	
	Hispanic	1.49 (1.03-2.17)	
Friends Smokers (Ref = None)	1	2.82 (2.05-3.88)	< 0.0001
	2	5.28 (3.82-7.30)	
	3 or more	10.47 (8.56-12.81)	
Siblings Smokers (Ref = None)	1	2.82 (2.29-3.48)	< 0.0001
	2	3.43 (2.59-4.54)	
	3 or more	7.07 (5.01-9.97)	
Parents/Guardians Smokers (Ref = None)	1	1.76 (1.44-2.15)	< 0.0001
	2	2.25 (1.82-2.79)	
	3 or more	3.63 (2.80-4.69)	
Weekly Personal Spending (Ref = Zero)	$1-$5	1.05 (0.72-1.53)	< 0.0001
	$6-$10	1.16 (0.81-1.68)	
	$11-$20	1.73 (1.28-2.34)	
	$21-$40	2.33 (1.75-3.09)	
	$41-$100	2.23 (1.65-3.00)	
	> $100	3.76 (2.93-4.81)	
Self-Esteem (Ref = High)	Low	1.66 (1.21-2.28)	0.0004
	Intermediate	0.87 (0.74-1.02)	

Flavoured Tobacco Use = 1 if: Menthol cigarette or Flavoured little cigar or cigarillo or Flavoured cigar or Flavoured tobacco in a water-pipe (hookah) was used over the past 30 days.
Flavoured Tobacco Use = 0 if: I did not use any of these things (above) in the last 30 days

Table 3.3: Factors associated with flavoured tobacco use by logistic regression analyses among 10–12 grade school students in Canada, 2012–2013 (n=13,139)

Variables		**Adjusted Odds Ratio (aOR) (95% CI: Lower to Upper)**	**p-value**
Ethnicity (Ref = White)	Black	0.94 (0.60-1.45)	0.0470
	Asian	0.65 (0.46-0.92)	
	Aboriginal	1.19 (0.88-1.60)	
	Hispanic	1.32 (0.84-2.08)	
Sex (Ref=Female)	Males	1.63 (1.36-1.95)	< 0.0001
Friends Smokers (Ref = None)	1	2.20 (1.62-2.99)	< 0.0001
	2	3.80 (2.71-5.31)	
	3 or more	7.08 (5.66-8.86)	
Siblings Smokers (Ref = None)	1	1.51 (1.22-1.88)	< 0.0001
	2	1.55 (1.09-2.20)	
	3 or more	3.40 (2.33-4.96)	
Weekly Personal Spending (Ref = Zero)	$1-$5	1.05 (0.68-1.62)	< 0.0001
	$6-$10	1.12 (0.71-1.76)	
	$11-$20	1.23 (0.87-1.76)	
	$21-$40	1.76 (1.26-2.45)	
	$41-$100	1.62 (1.17-2.26)	
	> $100	2.46 (1.82-3.33)	

Flavoured Tobacco Use = 1 if: Menthol cigarette or Flavoured little cigar or cigarillo or Flavoured cigar or Flavoured tobacco in a water-pipe (hookah) was used over the past 30 days.
Flavoured Tobacco Use = 0 if: I did not use any of these things (above) in the last 30 days

3.4 Discussion

This study sought to determine the prevalence and characteristics associated with the use of flavoured tobacco among a national sample of Canadian students in grades 10 through 12. It provides insight and adds knowledge to our understanding of flavoured tobacco use among youth in Canada along two discrete but interrelated perspectives/aspects (demographic and social).

From a demographic perspective, our study found that 14.8% of the students reported using flavoured tobacco. This is similar to the prevalence reported among high school students in the US[25] and previous studies in Canada.[6,26] Flavoured tobacco is becoming increasingly popular among students as evidenced by the fact that one out of every three Canadian youth has tried it[7] and sales have increased by eightfold in six years.[21] This may be a reflection of the widespread belief by youth that flavoured tobacco is a better alternative to regular tobacco, less harmful to their health and more fun to use.[15,27] Our findings also demonstrate a progressive rise in flavoured tobacco use with increasing grades 10–12 among Canadian students (16–18 years old). This is a period of identity development, increased curiosity and risk taking behaviour.[28] The tobacco industry, exploits the inherent vulnerability of this transitional period by focusing their trendy marketing and advertising campaigns on themes that resonate with youth such as independence, sophistication, fun and rebellion.[9]

In our study, male students were significantly more likely to use flavoured tobacco compared to females. This was consistent with evidence reported elsewhere in the literature.[11-13] It is possible that male students have higher risk-taking proclivities/behaviours along with easier access and higher affordability levels to flavoured tobacco when compared to females. Students who self-identified as Aboriginal or Hispanic did not have a statistically significant increased odds of using flavoured tobacco when compared to White students, but had a higher prevalence of use. Our results are corroborated by several Canadian studies that show an increased burden of smoking among Aboriginal youth.[29,30] However, there is not much in the literature detailing the smoking situation of Hispanic youth in Canada. This is an area that requires further study as evidence from Mexico[31,32] and the US[9,11] shows that Hispanic youth are at an increased risk for smoking behaviours, including the use of flavoured tobacco.[33]

From a social perspective, we found a significant association between the number of siblings or friends who smoke and the likelihood of a student using flavoured tobacco after adjusting for all other covariates. Interestingly, our study found peers to have a more pronounced influence on students' use of flavoured tobacco when compared to their siblings and even their parents/guardians. There are multiple mechanisms that may help explain this finding. It may be the result of the increased amount of time youth spend with their peers[34] and the opportunities for social learning,[35] ease of access to flavoured tobacco[35–37] and direct pressures to identify, bond and gain their respect and acceptance at this critical time of their development.[38]

Finally, we found that the more money a student had available to spend in a week, the higher the likelihood of them using flavoured tobacco. Several studies have associated youth's access to spending money with their risk of smoking.[6, 39, 40] A study in Ontario, Canada, found that even small differences in weekly spending allowance had an incremental and significant impact on the smoking status among youth. It reported that students who had less than $10 per week were significantly less likely to be smokers, those with $20 per week were significantly more likely to be experimental smokers, and students with more than $30 per week were significantly more likely to be current smokers.[40]

Study's strengths and limitations

Flavoured tobacco use as defined for the purposes of this study represented use in the past 30-days. This time limitation may not allow us to adequately determine the volume or frequency of use. Secondly, there were no objective measures of flavoured tobacco use since all the measures in the study were self-reports. Third, the YSS is a school-based survey and therefore, youth who do not attend school were excluded from our sample. Lastly, the study used of a cross-sectional design and therefore, it is unable to draw causal inferences between the variables studied and flavoured tobacco use. Despite the aforementioned limitations, this study also has several significant strengths. It used a national sample that was large in size and representative in scope and specifically looked to identify the prevalence and demographic and social characteristics in the use of flavoured tobacco among Canadian students in grades 10–12.

3.5 Conclusions

The results of our study show that flavoured tobacco use is a public health concern and has a strong appeal among youth in Canada. This is a particularly troubling finding, especially in light of the fact that there is a national ban on certain flavoured tobacco products. To be effective, strategies specifically tailored for youth using flavoured tobacco would require appropriate educational/prevention initiatives, more comprehensive legislation and better regulatory mechanisms. These interventions are urgently needed in order to prevent erosion and safeguard the significant gains made in our efforts to reduce smoking rates in Canada.

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CHAPTER 4: SEXUAL ORIENTATION AND SMOKING PREFERENCES: RESULTS FROM A POPULATION-BASED SURVEY IN CANADA 2009-2014[2]

Purpose: The purpose of this study was to use a large, representative, population-based survey to assess the characteristics and examine the associations between sexual orientation (heterosexual, lesbian/gay, or bisexual) and smoking status (current, former, and never smokers) among Canadians.

Methods: This is a cross-sectional study. It used and analyzed the combined data from the 2009-2014 Canadian Community Health Survey (CCHS). The primary outcome variable was cigarette smoking. The primary independent variable was sexual orientation. The independent variables included socio-demographics, environmental tobacco exposure and mental health status.

Results: This study found that the majority of bisexuals reported being current smokers (39.68%), while most lesbians/gays were former smokers (37.63%) and most heterosexuals were never smokers (40.65%). Multinomial logistic regression modeling found sexual orientation to be significantly associated with cigarette smoking. Specifically, bisexual females and lesbians were more likely to be current smokers rather than never smokers compared to heterosexual females (aOR: 2.68, 95% CI: 1.99-3.61 and aOR: 1.92, 95% CI: 1.29-2.85, respectively). There was no evidence to suggest that gay or bisexual males were more likely to be current smokers rather than never smokers compared to heterosexual males.

Conclusions: Sexual minority populations are diverse and highly vulnerable to smoking. The results of our study suggest that significant disparities in smoking exist within and between sexual minority and heterosexual populations.

Keywords: Sexual orientation; smoking; Canada

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[2] Bird Y, Wong J, **Mahmood R**, Nwankwo C, Moraros J. Sexual orientation and smoking: Results from a Population-Based Survey in Canada 2009-2014. Patient Prefer Adherence. February 2020. Submitted for publication, currently under review.

4.1 Introduction

Cigarette smoking remains a major public health concern. It is estimated that every year, approximately 40,000 Canadians[1] die due to smoking related diseases, leading to 16 billion dollars in total economic costs.[2] In 2015, approximately 5.4 million Canadians were either daily or occasional smokers.[3] Although there is extensive research on smoking prevalence and behaviours among the general population, there is limited research on the smoking preferences of sexual minorities in Canada with the majority of studies examining specific populations (i.e. youth, MSM, specific geographical areas). According to the 2012 Canadian Community Health Survey – Mental Health (CCHS-MH), 3.9% of Canadians reported being a sexual minority (specifically, lesbian, gay, or bisexual [LGB]).[4] Historically, sexual minority individuals are a vulnerable population that have been selectively targeted by the tobacco industry[5-8] and disproportionally impacted by tobacco-related diseases.[9]

Emerging research suggests that sexual minority individuals are at an increased risk for a number of adverse health behaviours, including cigarette smoking, when compared to heterosexuals.[10-12]

This may be of particular interest to tobacco prevention and control initiatives, as a growing body of evidence, mainly from the United States, found that sexual minority populations smoke cigarettes at significantly higher rates (20%-50%) than the national average (18%).[11-15] Specifically, it has been reported that sexual minority individuals have a higher prevalence of being current and former smokers,[16,17] start smoking at a younger age,[18] and smoke more frequently.[19,20] Within sexual minority subgroups, it has been noted that bisexuals smoke cigarettes at higher rates than their gay and lesbian counterparts.[21] In particular, bisexual women were found to have higher rates of cigarette use compared with lesbians, even after adjusting for other risk factors.[11,21,22]

The disparities found among and within sexual minority populations with regard to cigarette smoking may be attributed in part to issues of marginalization, discrimination, disclosure and internalized homophobia.[23] Studies have shown that sexual minorities are more likely to experience increased exposure to stress, stigma, depression, isolation, victimization, socialization in smoky areas, aggressive tobacco marketing, and substance use.[23-25] The minority stress theory posits that LGB individuals may use maladaptive coping behaviors because they experience

chronic, social and structural stressors, which helps explain the higher rates of cigarette use observed in this population.[26-28] However, as public levels of awareness and acceptance of homosexuality have increased in recent years,[29] the health disparities observed in cigarette smoking have been unevenly reduced, mainly benefiting gay men.[16] Lesbian and especially bisexual women are still two to three times more likely to smoke compared to heterosexual women.[30]

A few Canadian studies have investigated the link between sexual orientation and cigarette smoking preferences and found that LGB individuals are significantly more likely to smoke, when compared to their heterosexual peers.[9,10,31,32] One study reported that LGB adolescents had a higher prevalence of daily cigarette use (22%), when compared with their heterosexual counterparts (11%).[10] Another study found that lesbian and bisexual women were more likely to report daily smoking and other risky behaviors than heterosexual women.[9] However, these studies were limited by a number of factors including small sample sizes, assessment of the sexual minority population as a single aggregate group and/or evaluation of only specific subgroups (e.g. high school students, men who have sex with men), sex (women only) and/or geographic locations (e.g. Toronto, Greater Vancouver Area and Atlantic Canada). Therefore, the purpose of this study was to use a large, representative, population-based survey to assess the characteristics and examine the associations between sexual orientation (heterosexual, lesbian, gay, or bisexual) and smoking preferences (current, former, and never smokers) in Canada.

4.2 Methods

4.2.1 Instrument

This study used and analyzed the combined data from the 2009-2014 Canadian Community Health Survey (CCHS). CCHS is an annual, nationally representative, population-based survey, which uses a multistage stratified cluster probability sampling and aims to assess the health status, health service usage and determinants of health among people living in Canada.[33] This research was conducted at the Saskatchewan Research Data Centre (SKY-RDC), a part of the Canadian Research Data Centre Network (CRDCN). This service is provided through the support of the University of Saskatchewan, the Canadian Foundation for Innovation, the Canadian Institutes of Health Research, the Social Science and Humanity Research Council, and Statistics Canada. All views expressed in this work are our own.

4.2.2 Measures

Outcome variable: The outcome variable was cigarette smoking. In CCHS, smoking was assessed by asking participants to respond to whether they were: 1) daily, 2) occasional, 3) always occasional, 4) former daily, 5) former occasional and 6) never smokers. In this study, smoking was re-categorized as follows: 1) current smokers (daily, occasional or always occasional, past 30-day smokers), 2) former smokers (former daily or former occasional), and 3) never smokers (never).

Primary independent variable: The primary independent variable was sexual orientation (e.g. whether an individual self-identifies as gay, lesbian, bisexual, or heterosexual). Sexual orientation was determined for each participant based on their answer to the following survey question: “Do you consider yourself to be: heterosexual (sexual relations with people of the opposite sex), or homosexual (that is lesbian or gay, sexual relations with people of your own sex), or bisexual (sexual relations with people of both sexes).”

Other independent variables: In this study, selection of additional variables was based on review of the scientific literature[11,13,14] and included:

1. Socio-demographics: Age (18-29; 30-44; and 45-59 years old), sex (female, male), education (less than secondary school graduation; secondary school graduation; some post-secondary education; and post-secondary graduation), and relationship status (married or living common-law; widowed, separated or divorced; and single, never married).
2. Environmental tobacco smoke (ETS) exposure: Participants were asked to answer the following question: "Including both household members and regular visitors, does anyone smoke inside your home, every day or almost every day?" (Yes, No).
3. Mental health status: Participants were also asked to rate their mental health ("Excellent, Very Good, or Good and Fair or Poor"). Categories were collapsed similar to a previous study[4] into two groups: excellent, very good, or good; and fair or poor, due to cell size limitations.

4.2.3 Statistical analysis and model building

The analysis was conducted at the research data centre at the University of Saskatchewan (SKY-RDC). CCHS data from the 2009-2014 cycles were merged and analyzed using a pooled approach. The pooled approach (combined cycles from 2009-2014) was adopted because even though the CCHS has a large sample size, our analysis used a small population (sexual minorities) and using just one survey cycle would lead to poorer outcome estimation due to power, sampling error, and missing data.[34] Pooling involves combined the cycles from 2009, 2010, 2011, 2012, 2013 and 2014 into one large analytic sample.[35] Pooling of the cycles of the CCHS (2009-2014) was appropriate as the questions asked in these surveys were the same for the variables included (outcome and independent) and there was no changes in the coverage or sampling methodology over this time period.[35] The weights provided by the CCHS were scaled by a factor of 1/6 to account for the new analytic sample which serves as one large random sample derived from six initial random samples.[35] Pooling the CCHS cycles yielded a large enough sample size to conduct the analysis and provided sufficient power to provide higher quality estimates compared to using a single cycle.[35]

CCHS cycles are random-digit dialing telephone survey samples with computer-assisted interviewing. CCHS excludes First Nations members living on reserves, persons living in institutions (e.g., penitentiaries), and full-time members of the Canadian Armed Forces and the

Royal Canadian Mounted Police.[33] In our study, survey participants were Canadians ages 18-59 years old which is the measure used by the CCHS which is partially due to the sensitive nature of sexual orientation related questions and non-response by older adults, and is consistent with population based surveys with questions on sexual orientation conducted in the USA,[36] who answered all relevant questions on smoking status, sexual orientation, socio-demographics, ETS exposure and mental health status. The same questions were examined across all CCHS survey cycles to ensure they were consistently administered, coded and weighed. Individuals with missing data were excluded from our analysis (5.08%) (Figure 4.1).

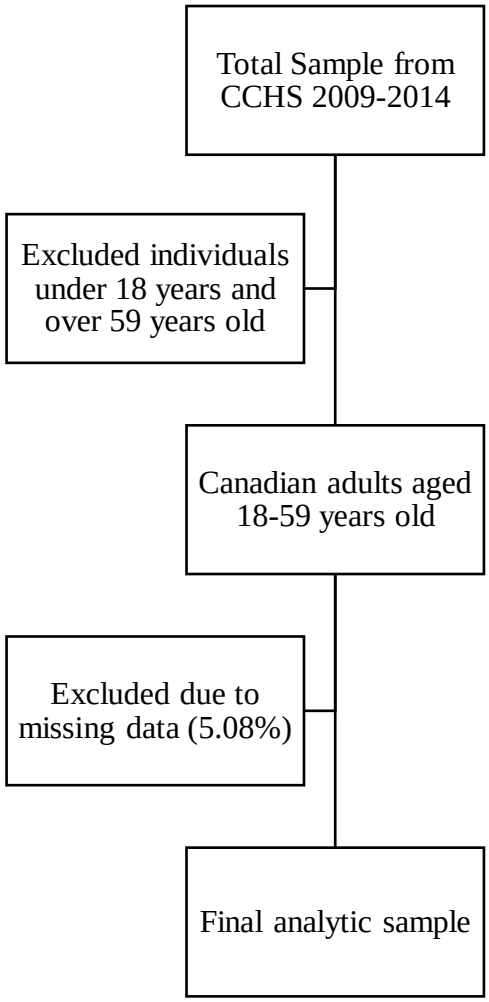

Figure 4.1: Flow diagram showing the final analytic sample from CCHS 2009-2014. Please note: Sample size numbers were not authorized for release due to confidentiality concerns by the Research Data Centre at the University of Saskatchewan (SKY-RDC).

Descriptive statistics and cross-tabulations were used to summarize the basic characteristics of the data. Univariable (unadjusted) analyses were conducted to determine whether there was an association between the outcome (smoking status) and the independent variables. Model selection was conducted using purposeful model selection.[37] Firstly, unadjusted analysis was conducted to determine the crude association between each of the independent variables and smoking status using a p-value ≤ 0.25 indicating statistical significance.[37] Variables that were statistically significant in unadjusted analysis were included in the initial multivariable model. Multivariable models were developed using multinomial logistic regression with manual backward elimination with a p-value ≤ 0.05 indicating statistical significance. When a variable was removed, confounding was assessed by comparing the values of the estimated regression coefficients (β) of the primary independent variable (sexual orientation) in each stage whereby $\Delta\beta \geq 20\%$ indicated confounding. If a variable was a confounder, it was kept in the model.[37]

Overall, three models were reported: Model 1 - examined the unadjusted (crude) association between smoking status and sexual orientation. Model 2 - examined the association between smoking and sexual orientation, while adjusting for the effects of age and sex. Model 3 - examined the association between smoking and sexual orientation, while adjusting for the effects of socio-demographics, exposure to ETS and mental health status. Goodness of fit of the models was assessed by examining deviance and Pearson chi-square statistics similar to previous multinomial logistic regression models.[38,39] Datasets were merged using SPSS Statistics software version 24.0 (IBM Corp., Armonk, NY, USA), while analysis was conducted using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

4.3 Results

4.3.1 Descriptive statistics

In this study, we report our findings on a final, analytic, weighted sample of approximately 390,000 participants, which represents approximately 19 million Canadians. Of these, approximately 2.5% of Canadians aged 18-59 years old, identified as being sexual minorities and specifically, 1.4% reported being lesbians/gays and 1.1% reported being bisexual. This is in line with the nationally reported rates of sexual minorities in Canada.[40]

The frequency distributions by smoking status for sexual orientation and other independent variables (age, sex, education, relationship status, environmental tobacco smoke, mental health and income) overall and stratified by sex are presented in Table 4.1. Bisexuals (39.68%) had the highest prevalence of current smokers followed by homosexuals (31.37%) and heterosexuals (23.82%). Individuals aged 18-29 years old had the highest rates of current smokers (25.94%) when compared to respondents aged 30-44 years old (23.32%) and 45-59 years old (23.25%). A higher proportion of males were current smokers (27.60%) compared to females (20.44%). Survey respondents with less than secondary school graduation had the highest prevalence of current smokers (44.18%) compared to those who reported secondary school graduation (28.99%), some post-secondary school education (27.36%) and post-secondary graduation (19.20%). Individuals who were widowed or divorced or separated had higher rates of current smokers (34.80%) when compared to those who were single, never married (29.23%) and married or common law (20.04%). Respondents who were exposed to environmental tobacco smoke reported higher rates of current smoking (62.59%) compared to those who did not (16.33%). Individuals reporting fair or poor mental health had a higher prevalence of current smokers (39.38%) compared to those reporting excellent or very good or good mental health (23.09%) (Table 4.1).

The frequency distributions by sexual orientation for smoking status and other independent variables (age, sex, education, relationship status, environmental tobacco smoke, mental health and income) are presented in Table 4.2. Most heterosexuals (37.76%) and lesbians/gays (38.86%) were aged 45-59 years old, while 53.90% of bisexuals were aged 18-29 years old. There were more gays (62.90%) than lesbians (37.10%), while most bisexuals were females

(69.90%). When looking at the relationship status, the majority of heterosexuals reported being either married or living in a common-law relationship (62.80%), while most gays/lesbians (56.67%) and bisexuals (60.40%) were single. When examining education, bisexuals reported the lowest rates of post-secondary graduation (48.88%). Bisexuals also reported the highest rate of exposure to ETS (16.39%), followed by guys/lesbians (12.52%) and then heterosexuals (9.58%). Finally, bisexuals reported the highest proportion of individuals with fair or poor mental health (18.61%) (Table 4.2).

Table 4.1: Descriptive statistics by smoking status

		Entire Population			Females			Males			Total (Weighted)
		Current Smoker n=4605955	Former Smoker n=6787804	Never Smoker n=7721950	Current Smoker n=2038293	Former Smoker n=3352990	Never Smoker n=4578617	Current Smoker n=2747794	Former Smoker n=3656506	Never Smoker n=3552075	
Primary Variable											
Sexual Orientation (n=19130000)	Heterosexual	23.82%	35.53%	40.65%	20.20%	33.98%	45.82%	27.44%	37.09%	35.47%	18660000
	Lesbian/Gay	31.37%	37.63%	31.01%	27.38%	42.35%	30.27%	33.72%	34.84%	31.44%	268249
	Bisexual	39.68%	30.63%	29.69%	40.41%	30.33%	29.26%	38.00%	31.32%	30.69%	209715
Other Variables											
Age (n=19130000)	18-29 years old	25.94%	23.74%	50.32%	21.57%	22.90%	55.53%	30.20%	24.57%	45.24%	5298413
	30-44 years old	23.32%	34.86%	41.81%	19.31%	33.56%	47.13%	27.36%	36.18%	36.46%	6649453
	45-59 years old	23.25%	43.84%	32.91%	20.67%	41.39%	37.94%	25.88%	46.32%	27.80%	7186998
Biological Sex (n=19130000)	Female	20.44%	33.63%	45.92%							9580310
	Male	27.60%	36.73%	35.68%							9554554
Education (n=18990000)	Less Secondary School Grad.	44.18%	27.93%	27.89%	39.16%	25.63%	35.21%	48.04%	29.70%	22.26%	1661265
	Secondary School Grad.	28.99%	31.90%	39.11%	25.27%	31.68%	43.05%	32.50%	32.10%	35.40%	3587156
	Some Post-Secondary	27.36%	30.39%	42.24%	24.84%	28.66%	46.49%	29.86%	32.11%	38.03%	1445533
	Post-Secondary Grad.	19.20%	37.81%	42.98%	16.31%	35.85%	47.84%	22.28%	39.90%	37.82%	12300000
Relationship Status (n=19100000)	Married/Common-Law	20.04%	40.17%	39.78%	16.80%	37.84%	45.37%	23.36%	42.56%	34.08%	11860000
	Widowed/Divorced/Separated	34.80%	36.26%	28.94%	30.71%	36.23%	33.06%	41.42%	36.31%	22.27%	1597068
	Single, Never Married	29.23%	24.55%	46.22%	24.92%	23.04%	52.04%	32.85%	25.83%	41.32%	5646443
Environmental Tobacco Smoke (n=18360000)	Yes	62.59%	18.38%	19.02%	61.16%	17.49%	21.35%	63.93%	19.22%	16.85%	1778481
	No	16.33%	38.62%	45.05%	13.56%	36.44%	50.00%	19.20%	40.87%	39.93%	16580000
Mental Health (n=19110000)	Excellent, Very Good, Good	23.09%	35.64%	41.27%	19.43%	34.15%	46.42%	26.73%	37.12%	36.15%	17980000
	Fair or Poor	39.38%	30.48%	30.14%	36.12%	29.14%	34.73%	43.29%	32.10%	24.61%	1131641

Table 4.2: Descriptive Statistics by Sexual Orientation

		Heterosexual (n=18660000)	Lesbian/Gay (n=268249)	Bisexual (n=209715)	Total (Weighted)
Outcome Variable					
Smoking Status (n=19120000)	Current Smoker	23.82%	31.37%	39.68%	4605955
	Former Smoker	35.53%	37.63%	30.63%	6787804
	Never Smoker	40.65%	31.01%	29.69%	7721950
Independent Variables					
Age (n=19130000)	18-29 years old	27.35%	30.71%	53.90%	5298413
	30-44 years old	34.89%	30.43%	27.73%	6649453
	45-59 years old	37.76%	38.86%	18.37%	7186998
Sex (n=19130000)	Female	50.03%	37.10%	69.90%	9580310
	Male	49.97%	62.90%	30.10%	9554554
Education (n=18990000)	Less Than Secondary School Graduation	8.75%	4.75%	13.78%	1661265
	Secondary School Graduation	18.89%	14.54%	24.00%	3587156
	Some Post-Secondary	7.55%	7.42%	13.35%	1445533
	Post-Secondary Graduation	64.81%	73.28%	48.88%	12300000
Relationship Status (n=19100000)	Married/Common-Law	62.80%	36.49%	30.37%	11860000
	Widowed/Divorced/Separated	8.37%	6.84%	9.23%	1597068
	Single, Never Married	28.82%	56.67%	60.40%	5646443
Environmental Tobacco Smoke (n=18360000)	Yes	9.58%	12.52%	16.39%	1778481
	No	90.42%	87.48%	83.61%	16580000
Mental Health (n=19110000)	Excellent, Very Good, or Good	94.26%	91.39%	81.39%	17980000
	Fair or Poor	5.74%	8.61%	18.61%	1131641

4.3.2 Multinomial logistic regression models

Three models are presented using multinomial logistic regression analyses to examine the association between sexual orientation and smoking overall, among females and among males (Model 1: unadjusted, Model 2: adjusted for age and sex and Model 3: adjusted for socio-demographics, exposure to ETS and mental health status). The results are presented in Table 4.3.

Model 1: This model examined the unadjusted association between smoking and sexual orientation. Sexual orientation was significantly associated with smoking. Specifically, lesbians/gays were more likely to be current smokers than never smokers (OR: 1.42, 95% CI: 1.41-1.44) and former smokers than never smokers (OR: 1.38, 95% CI: 1.36-1.39) compared to heterosexuals. Additionally, bisexuals were more likely to be current smokers rather than never smokers (OR: 2.23, 95% CI: 2.20-2.25) and former smokers than never smokers (OR: 1.19, 95% CI: 1.18-1.21) compared to heterosexuals. Bisexual females were more likely to be current smokers than never smokers (OR: 3.10, 95% CI: 3.06-3.14) and former smokers than never smokers (OR: 1.42, 95% CI: 1.40-1.43) compared to heterosexuals. Bisexual males were more likely to be current smokers than never smokers (OR: 1.44, 95% CI: 1.41-1.47). The large sample size used in this analysis likely contributes to the narrow 95% confidence intervals seen in the unadjusted models, as increasing sample size decreases the width of confidence intervals.

Model 2: This model examined the association between smoking and sexual orientation, while adjusting for the effects of age and sex. It found that lesbians were more likely to be current smokers rather than never smokers (aOR: 1.90, 95% CI: 1.23-2.93) and former smokers rather than never smokers (aOR: 1.99, 95% CI: 1.37-2.88) compared to heterosexuals. Bisexual females were more likely to be current smokers rather than never smokers (aOR: 3.30, 95% CI: 2.38-4.56) and former smokers rather than never smokers (aOR: 1.89, 95% CI: 1.35-2.64) compared to heterosexuals. There was no evidence to suggest that gay or bisexual males were more likely to be current smokers rather than never smokers compared to heterosexual males.

Model 3: This model examined the association between smoking and sexual orientation, while adjusting for the effects of socio-demographics, exposure to ETS and mental health status.

Results showed that lesbians were more likely to be current smokers than never smokers (aOR: 1.92, 95% CI: 1.29-2.85) and former smokers than never smokers (aOR: 2.11, 95% CI: 1.54-2.89) compared to heterosexuals. Bisexual females were more likely to be current smokers rather than never smokers (aOR: 2.68, 95% CI: 1.99-3.61) and former smokers than never smokers (aOR: 1.95, 95% CI: 1.47-2.59) compared to heterosexuals. There was no evidence to suggest that gay or bisexual males were more likely to be current smokers than never smokers or former smokers than never smokers compared to heterosexual males.

Table 4.3: Multinomial logistic regression models examining the association between smoking and sexual orientation

		Entire Population (n=18,157,938)		**Females** (n=9,203,962)		**Males** (n=8,953,976)	
		Current[a] vs. Never Smoker[c] OR (95% CI)	Former[b] vs. Never Smoker OR (95% CI)	Current vs. Never Smoker OR (95% CI)	Former vs. Never Smoker OR (95% CI)	Current vs. Never Smoker OR (95% CI)	Former vs. Never Smoker OR (95% CI)
Model 1[*]							
Sexual Orientation (Ref: Heterosexual)	Lesbian/Gay	1.42 (1.41-1.44)	1.38 (1.36-1.39)	1.88 (1.85-1.91)	1.90 (1.87-1.93)	1.09 (1.07-1.10)	1.04 (1.03-1.05)
	Bisexual	2.23 (2.20-2.25)	1.19 (1.18-1.21)	3.10 (3.06-3.14)	1.42 (1.40-1.43)	1.44 (1.41-1.47)	*0.98 (0.96-1.00)*
Model 2[**]							
Sexual Orientation (Ref: Heterosexual)	Lesbian/Gay	*1.35 (0.99-1.85)*	1.38 (1.04-1.82)	1.90 (1.23-2.93)	1.99 (1.37-2.88)	*1.09 (0.83-1.44)*	*1.07 (0.84-1.38)*
	Bisexual	2.61 (1.88-3.61)	1.66 (1.19-2.31)	3.30 (2.38-4.56)	1.89 (1.35-2.64)	*1.47 (0.96-2.25)*	*1.14 (0.75-1.74)*
Model 3[***]							
Sexual Orientation (Ref: Heterosexual)	Lesbian/Gay	1.49 (1.18-1.90)	1.48 (1.21-1.80)	1.92 (1.29-2.85)	2.11 (1.54-2.89)	*1.30 (0.99-1.71)*	*1.16 (0.92-1.47)*
	Bisexual	2.24 (1.75-2.88)	1.69 (1.33-2.14)	2.68 (1.99-3.61)	1.95 (1.47-2.59)	*1.37 (0.89-2.11)*	*1.18 (0.79-1.74)*

[a] *Current smoker denotes daily, occasional or always occasional smokers*
[b] *Former smoker denotes former daily or former occasional*
[c] *Never smoker denotes never smoked*
[*] *Model 1: Unadjusted OR for smoking status by sexual orientation*
[**] *Model 2: aOR for smoking status by sexual orientation adjusting for age and sex for entire population; female and male model similar except for the sex variable*
[***] *Model 3: aOR for smoking status by sexual orientation adjusting for age, sex, education, relationship status, exposure to environmental tobacco smoke and mental health status; female and male model similar except for the sex variable*
Note: Weighted sample sizes presented; OR = odds ratio; aOR = adjusted odds ratio; CI = confidence interval; Ref = reference group; italics indicates not significant (p-value ≥ 0.05)

4.4 Discussion

To the best of our knowledge, this is the first population-based study to examine cigarette smoking and explore for differences across sexual orientation, age and sex among adult Canadians. This study builds upon our limited knowledge on cigarette smoking and health disparities among sexual minorities in Canada. It helps inform and potentially guide uniquely tailored tobacco cessation and prevention efforts to benefit LGB subpopulations, which are at higher risk for cigarette smoking and negative health outcomes and yet have been largely overlooked and understudied in the scientific literature.

In our study, lesbians/gays (31.4%) and bisexuals (39.7%) had a higher proportions of being current smokers, when compared to heterosexuals (23.8%). Our findings are supported by previous studies, which show lesbians/gays and especially bisexuals to have higher rates of smoking, when compared to heterosexuals.[11,41-43]

Biological sex and sexual orientation differences in cigarette smoking emerged in our study. Among females, lesbians were approximately two times more likely to be current smokers rather than never smokers, when compared to heterosexual females. Similarly, this association was nearly three times more likely among bisexual females, when compared to heterosexual females. Our findings are corroborated by those reported in previous studies.[24,44] When examining males, we did not find a statistically significant association between sexual orientation and smoking. There is conflicting evidence in the literature regarding the influence of sexual orientation on smoking among males with certain studies suggesting an association exists,[18,45] while other studies suggest there is no association.[42,46] However, when we looked at the proportion of male current smokers in our study, gays and bisexuals had a higher prevalence of smoking than heterosexuals.

Our study results show that even after controlling for known risk factors (education, relationship status, ETS exposure and mental health status), sexual orientation remained significantly associated with smoking among females (lesbian and bisexual) but not for males (gay and bisexual). There are different possible explanations for these biological sex-based differences. Female sexual minorities may have a dual-disadvantaged status by being both a sexual minority and female[25] leading to increased stressors compared to male sexual minority counterparts.

Lesbian and bisexual women are disproportionately more susceptible to being influenced by tobacco marketing compared to heterosexual women, while similar trends are not seen among gay and bisexual men.[47] While a study found that bisexual and lesbian women reported smoking their first cigarette at younger ages than heterosexual women and this relationship was significantly more pronounced compared to what was seen among men.[18] This is an important finding as research has shown that the majority of adult smokers started smoking as teenagers and a younger age of smoking onset increases the risk of daily smoking, smoking intensity, nicotine dependence and results in more difficulties in smoking cessation.[25,48] Dual disadvantage theory, tobacco marketing and age of smoking their first cigarette are all factors that may partially explain the biological sex-based disparities observed in the LGB community.

We found that bisexual females in particular have a higher prevalence of cigarette use, even when compared with lesbian women and gay or bisexual men. These results help confirm previous findings that bisexual women may be at highest risk[11,22,49] and support the hypothesis that there is within-group variation in cigarette use among the sexual minority subpopulations, even after adjusting for demographic and socioeconomic factors.[11,14] When examining differences between lesbian and bisexual women, bisexual women have different demographic characteristics and one study found they have a different psychosocial profile which may lead to increased tobacco use.[50]

This has important implications for tobacco control policy and practice, pointing to the need to generally, increase outreach efforts within the sexual minority communities and specifically, consider tailoring messaging toward its most vulnerable subgroup, bisexual women.

Implications for public health research

In Canada, there is paucity of population-based studies that provide insight and improve our understanding into sexual minority health and risky behaviours, including cigarette smoking. Our study findings are seminal in scope and context within the Canadian population. Future research efforts need to focus on several key areas. It will be important to study whether the adult smoking behaviours we observed in our study, start at an early age among sexual minorities in Canada and identify the mediators that support it into adulthood. Additionally, the heterogeneity in cigarette smoking according to sex and sexual orientation underscores the need to design

surveys that permit us to study the unique risk factors that are associated with the observed disparities among intragroup sexual minorities (lesbians/gays vs bisexuals vs heterosexual), better measure the multiple dimensions of sexual orientation (sexual behaviour, sexual attraction and sexual identity), and consider between-sex differences among additional subpopulations (transsexual, transgender, queer and two-spirited) and ethnic groups (White, Black, Asian, Arab, Latino and Aboriginal) in Canada.

Strengths and limitations

The several strengths of this study. This study helps highlight the inadequacy in using the terms "sexual minority" or "LGB" to broadly group different heterogeneous populations together even though they are unique in composition, behaviour and risk profile for cigarette smoking. Additional strengths include the use of a randomly selected, probability-based, Canadian-wide population sample that directly asks about sexual orientation. It uses a previously validated survey design and examines an important issue among highly vulnerable sexual minority populations. A limitation of this study was the low frequency of self-reported sexual minority individuals in Canada. To address this limitation, we had to re-categorize some variables to improve effect estimates but it limited the ability to incorporate additional variables. The survey only asked about sexual identity but research has shown that attention also needs to be directed to sexual attraction and sexual behaviors.[51] Our study is cross-sectional in design and therefore, it permits us to report on possible associations but it is unable to determine causal relationships between smoking and sexual orientation. Further research with longitudinal studies is warranted. Finally, individuals may be reluctant to self-report being sexual minorities due to low supports, social stigma, fear of discrimination, social desirability, issues related to disclosure, or the private and personal nature of the question. Therefore, it is possible that the sexual minority population is under-reported in this study.

4.5 Conclusion

Sexual orientation minority populations are diverse and highly vulnerable to smoking. The results of our study suggest that significant disparities in smoking exist within and between sexual minority and heterosexual populations. Additionally, bisexuals and lesbians/gays in Canada have different risk profiles for smoking and provide compelling evidence for designating the sexual minority community as a priority population for tobacco control, prevention and cessation efforts. To help reduce the burden of smoking among sexual minorities, family physicians, primary healthcare providers, policymakers and advocates need to use community-based outreach strategies and implement interventions that are culturally sensitive, appropriate and tailored to meet the specific needs of this increasingly diverse community.

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CHAPTER 5: EXAMINING THE PREVALENCE AND ASSOCIATION BETWEEN E-CIGARETTE USE AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE IN CANADA: A CROSS-SECTIONAL STUDY[3]

Introduction: E-Cigarette use is a growing public health concern with 863,000 Canadian past 30-day users, defined as individuals who have used an e-cigarette in the past 30-days. While there are potential health consequences related to e-cigarettes, their use continues to grow. COPD is an irreversible lung condition characterized by limitation of the respiratory airways and systemic inflammation. Conventional tobacco use is the dominant cause of COPD. There are proposed mechanisms linking e-cigarette use to COPD. The purpose of this study was: 1) To determine the prevalence of e-cigarette use among COPD patients; 2) to determine the independent association between e-cigarette use and COPD status; 3) to determine the association between dual e-cigarette and conventional tobacco use on COPD and 4) to investigate the role of sex as an effect modifier.

Methods: This study is a cross-sectional drawing data from the Canadian Community Health Survey (CCHS) 2015-2016. Weighted logistic regression analysis examined the relationship between e-cigarette use and self-reported COPD status and dual e-cigarette/conventional tobacco use and self-reported COPD while adjusting for other independent variables.

Results: Individuals aged 35 years old or older (n=37,754) had an overall prevalence of COPD of 5.70%, while among past 30-day e-cigarette users, the prevalence increased to 15.13%. The association of past 30-day e-cigarette use with COPD was statistically significant and modified by sex with females (aOR=3.00, 95% CI: 2.95-3.05) having a higher association than males (aOR=1.47, 95% CI: 1.43-1.50). Dual past 30-day e-cigarettes and current tobacco users were more likely to report COPD (aOR=14.16, 95% CI:13.91-14.42) compared to individuals using neither product.

Conclusions: There is an independent association between e-cigarette use and COPD, which is modified by sex. Dual use of e-cigarette/conventional tobacco has a stronger association with COPD compared to either single product use.

Keywords: E-cigarettes, tobacco smoking, COPD, Canada

[3] **Mahmood R**. et. al. Examining the prevalence and association between e-cigarette use and chronic obstructive pulmonary disease in Canada: A cross-sectional study. Manuscript under preparation for submission.

5.1 Introduction

Electronic cigarettes (e-cigarettes) are battery-operated handheld electronic nicotine-delivery systems (ENDs). The vapor produced contains different flavorings, chemicals, nicotine concentration and is smokeless.[1] Since their global introduction in 2006, there has been exponential growth and increasing popularity, especially among youth.[2] Similar to strategies employed resulting in flavored tobacco becoming the preferable tobacco product among youth,[3,4] e-cigarettes have been marketed as safe, healthier than tobacco, and tobacco cessation devices designed to appeal as safe alternatives to conventional tobacco use.[2,5] E-cigarettes have been marketed as a device that satisfies the need of nicotine for tobacco smokers while reducing or eliminating the disadvantages related to combustion and tar in tobacco smoke.[6] However, studies on both tobacco smokers and e-cigarette users have found many differentially expressed proteins in airway epithelium tissue including proteins involved in immunomodulatory activities that contribute to respiratory disease pathogenesis.[7,8]

The e-cigarette industry in 2018 was estimated to be worth $15.7 billion and continues to grow, and projected to be worth approximately $40 billion by 2023.[9] In Canada, approximately 4.6 million (15.4%) Canadians reported ever e-cigarette use, and 863,000 (2.9%) were classified as past 30-day e-cigarette users.[10] Interestingly, tobacco users had the highest rate of e-cigarette use, with 54.1% of current smokers reporting ever use and 12.2% reporting past 30-day use, which might be more harmful, resulting in worse respiratory health outcomes.[6,10] Additional Canadian trends show increased e-cigarette uptake and use among males, youth, and young adults and for tobacco cessation (23.6%), which might delay or prevent tobacco cessation entirely.[6,10] Among US high school and middle school students, past 30-day e-cigarette users in 2018 had significantly increased compared to 2011, while past 30-day use of any tobacco product has not considerably changed during this period.[11] This rise in the past 30-day use of e-cigarettes could be attributed to appealing characteristics of e-cigarettes such as more nicotine content, discrete and attractive shapes of the devices, and appealing flavorings.[11] Moreover, there is cumulative evidence that e-cigarette use among youth is related to a higher risk of ever use of tobacco products.[6] With the rapid growth in e-cigarette use and their relatively recent introduction, both short term and long-term health consequences are not fully understood. There is growing evidence of negative health outcomes, including cardiotoxicity,[12,13] immune dysfunction,[12]

cerebrotoxicity,[13] osteotoxicity,[14,15] nicotine addiction,[13,16] and mental health issues.[17] Preclinical and clinical experiments have shown that e-cigarette use causes chronic pulmonary inflammation and suppressed immune response which is linked to negative respiratory health outcomes such as chronic obstructive pulmonary disease (COPD).[13,18-20]

COPD is an irreversible lung condition, including both chronic bronchitis and emphysema. It is characterized by limitation of the respiratory airways and systemic inflammation with symptoms such as sputum production, chronic cough, and shortness of breath.[21] This inflammatory response is strongly associated with cigarette smoking stress and only partially responds to anti-inflammatory medicines, with smoking cessation improving prognosis.[22] COPD has a global prevalence of 65 million and is predicted to become the third leading cause of death worldwide by 2030.[23] The dominant cause of COPD is tobacco smoking.[24] The pathogenesis of COPD through tobacco smoke inhalation is through multiple different mechanisms including increased lung inflammation, the protease/anti-protease theory, abnormal elastin synthesis, and repair, reactive oxygen species (ROS) mediated alveolar damage, epigenetic changes and through exposure to nicotine which acts on nicotinic-acetylcholine receptors.[25-27]

Studies show women are more susceptible to developing COPD at younger ages possibly due to a faster annual decline in FEV_1 percent compared to males, differences in genetics, levels of female sex hormones, cytokine expression, nicotine metabolism and the development of COPD symptoms at lower levels of tobacco exposure compared to males.[24,28,29] Furthermore, evidence suggests that sex differences influence the clinical presentation of COPD, which was once considered a male dominant disease, with women being diagnosed at younger ages, having more morbidities, hospitalizations, and in-hospital deaths than men and often remaining undiagnosed due lack of proper evaluation.[29,30] Since 2000, in the United States, the majority of deaths attributed to COPD are among females, with a continuing narrowing gap in the age-adjusted death rate between males and females.[30] Environmental tobacco smoke exposure has been shown to be an independent, modifiable risk factor for COPD, both associated with its severity and incidence, possibly due to synergy with tobacco use and due to chronic inflammation and airway obstruction attributable to airway irritation from particulate matter in tobacco smoke, especially in homes.[31-33]

Studies examining the relationship between e-cigarette use and COPD have been conducted in vitro and in animal models finding that inhaled nicotine exposure using e-cigarette solutions affected cytokine expression, impaired mitophagy and increased lung cellular senescence, airway hyper-reactivity, lung tissue destruction, emphysema, impaired mucociliary clearance, increased risk of infections all potentially leading to the development of COPD[34-38] potentially as toxic as tobacco exposure.[39] Several human studies have been conducted to examine if a relationship between e-cigarette use and COPD exists. A population-based study suggested that an independent association between former and current e-cigarette use and COPD exists even when adjusting for smoking status with increased e-cigarette use (dose), leading to a stronger association with COPD.[18,19,40] Moreover, additional findings point to dual users of e-cigarettes and tobacco having the strongest association with the development of the respiratory disease, higher nicotine dependence, and using more nicotine than conventional tobacco smokers.[19,41]

Based on a literature review and the increasing trends in Canadian e-cigarette use, the objectives of this study are to: 1) to determine the prevalence of e-cigarette use among COPD patients; 2) to determine the association between e-cigarette use and COPD status; 3) to determine the association between dual e-cigarette and conventional tobacco use on COPD and 4) to investigate the role of sex as an effect modifier.

5.2 Methods

5.2.1 Study design

The data used in this study was from the Canadian Community Health Survey (CCHS) 2015-2016 Public Use Microdata Files (PUMFs) data, made available to bona fide researchers through the Data Liberation Initiative (DLI) of Statistics Canada. It is anonymized survey data devoid of any personally identifying information. The secondary analysis of such data does not require ethical clearance. Participants in the original survey signed an informed consent and voluntarily participated in the survey. The original survey received ethical approval through Statistics Canada procedures. Cross-sectional studies allow the analysis of large samples to determine if an association exists between the exposure (e-cigarette use) and outcome (COPD status); however, causality cannot be inferred.[42] As cross-sectional studies are relatively inexpensive and faster to conduct, they can provide background or exploratory results to inform future longitudinal studies incorporating cause and effect and temporality.

The CCHS is an annual cross-sectional survey providing information on the health status, healthcare utilization, and health determinants of the Canadian population.[43] The primary use for the CCHS is for health surveillance and population health research.[43] The CCHS 2015-2016 covers the Canadian population aged 12 years old and older, all ten provinces and three territories and excludes the following groups who represent approximately 3% of the Canadian population: individuals who live on reserves and other Aboriginal settlements in the provinces, full-time members of the Canadian armed forces, institutionalized individuals, children aged 12-17 years old living in foster care and the Region du Nunavik and Region des Terres-Cries-de-la-Baie-James health regions in Quebec.[43] The CCHS is produced by the Health Statistics Division, Statistics Canada.[43]

The CCHS samples the population using a multi-stage allocation strategy based on the population of each age group, province, and the health region within each province. There are two different frames used in sampling.[43] Overall the response rate for the 2015-2016 CCHS was 59.6% (185,176 selected, 110,095 responded).[43] Survey weights were calculated and provided to increase generalizability from the sample to the general population.[43]

5.2.2 Study sample

E-cigarette use was assessed as optional content in the 2015/2016 CCHS in Ontario, British Columbia, Nova Scotia and the Northwest Territories. Of the 109,659 participants surveyed, 37,754 remained after excluding individuals not in the provinces surveyed on e-cigarette use, under the age of 35 years old, and due to missing data (COPD status, e-cigarette use, smoking status, age, sex, education, alcohol use and exposure to environmental tobacco smoke; 2.81%) (Figure 5.1).

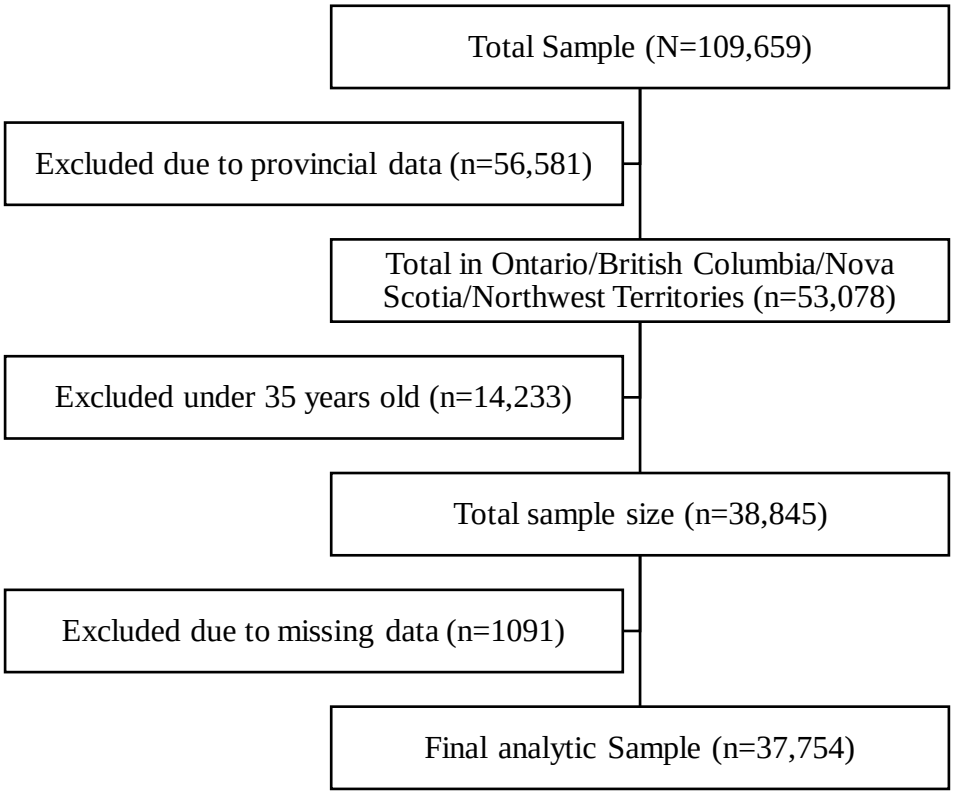

Figure 5.1: Flow diagram showing the final analytic sample from CCHS 2015-2016.

5.2.3 Outcome, primary independent and other independent variables

The multiple tobacco products use theoretical framework[44,] and a literature review was used in identifying and selecting factors included in the analysis. This framework helps to better understand the influence of e-cigarettes compared to conventional tobacco smoking, and how they impact health outcomes such as COPD.[44]

The outcome variable for this study was self-reported COPD status (yes/no), representing the effect on health in the multiple tobacco product use framework. This question was administered to individuals aged 35 years old or older asking if the respondent has chronic bronchitis or emphysema or chronic obstructive pulmonary disease or COPD.

The primary independent variable (product in multiple tobacco use framework) was past 30-day e-cigarette use (yes/no). Participants were asked if they used an electronic cigarette or e-cigarette in the past 30-days.

Other independent variables related to COPD including person-level factors (age, sex and educational status (socioeconomic status indicator)), situational factors (alcohol consumption and exposure to environmental tobacco smoke), and products (tobacco cigarette use) were included. Age was recategorized as individuals aged 35-49 years old, 50-65 years old and 65 years or older. Sex was reported as biological sex (male or female). Educational status served as an indicator of socioeconomic status, with the highest level of education reported (Less than secondary school graduation or Secondary school graduation, no post-secondary education or Post-secondary certificate diploma or university degree). Alcohol use was assessed by self-reported past 12-month type of drinker (regular drinker, occasional drinker, and did not drink in the last 12 months). Environmental tobacco smoke (ETS) exposure was assessed by asking if someone smokes inside the home every day (yes/no). Smoking status was recategorized into individuals who were current tobacco smokers (current daily smokers or current occasional smokers; individuals who smoked at least 100 cigarettes in their lifetime and smoked a cigarette in the past 30 days), former tobacco smokers (former daily smokers or former occasional smokers or experimental smokers who smoked at least one cigarette but not in the past 30 days) and never tobacco smokers (lifetime abstainer, never smoked a whole cigarette).

To address the association between dual use of tobacco and e-cigarettes and COPD, we recategorized past 30-day e-cigarette use and smoking status into a dual use variable with the following levels: 1) Past 30-day e-cigarette and current tobacco user; 2) Past 30-day e-cigarette and former tobacco user; 3) Past 30-day e-cigarette and never tobacco user; 4) No past 30-day e-cigarette use and current tobacco user; 5) No past 30-day e-cigarette use and former tobacco user; and 6) No past 30-day e-cigarette use and never tobacco user.

5.2.4 Statistical methods

Descriptive statistics were calculated by examining the prevalence of COPD by each factor included in this study (past 30-day e-cigarette use, person-level factors, situational factors, and products). Past 30-day e-cigarette use by smoking status was examined to ascertain dual use, and both past 30-day e-cigarette and current tobacco use by age group to examine potential trends in use by age.

In order to examine the association between COPD status and the past 30-day e-cigarette use, survey weights[43] provided in the CCHS were applied to account for the sampling strategy and to improve generalizability of the results. The purposeful selection of covariates methodology was used.[45] When determining the crude association (unadjusted) between the primary independent variable (past 30-day e-cigarette use) and the outcome variable (COPD status) as well as between the remaining independent variables and COPD status, an initial cut-off value p-value of 0.25[46] was used to assess if variables were to be kept in the final model. If the crude association was found to be significant (p-value ≤ 0.25), these variables were kept for multivariable logistic regression modeling. Models were developed using backward elimination with a p-value ≤ 0.05 indicating statistical significance. As variables were removed, confounding was assessed by examining if the change in the regression coefficient of the primary independent variable changed by more than 20% ($\Delta\beta \geq 20\%$ indicated confounding). Variables that were not confounders were removed from the model. Multicollinearity was assessed using a variance inflation factor (VIF) of 2.5 as the cut of value, with values greater than 2.5, indicating multicollinearity.[45] For the models using past 30-day e-cigarette use as the primary independent variable, all two-way multiplicative interactions were assessed using a p-value of 0.05. Model fitness was assessed using the Hosmer-Lemeshow goodness of fit test with a p-value ≥ 0.05, indicating the model is a good fit for the data.[46] Data analysis was conducted using SAS 9.4.

5.3 Results

5.3.1 Descriptive statistics

The overall prevalence of COPD was 5.70% (n=37,754). Among past 30-day e-cigarette users, the prevalence of COPD was 15.13%. Dual users (past 30-day e-cigarette users and current tobacco users) had a prevalence of COPD of 14.74%. Individuals by the other independent variables with the highest prevalence of COPD were the oldest age group (8.62%), females (6.10%), the lowest level of educational attainment (10.72%), no past 12-month alcohol consumption (8.52%), exposure to environmental tobacco smoke (14.56%) and current smokers (11.28%) (Table 5.1).

When examining the relationship between past 30-day e-cigarette use and tobacco smoking, the majority of past 30-day e-cigarette users were current tobacco users (70.38%) (Figure 5.2). The largest proportion of past 30-day e-cigarette users (n=800) were in the youngest age group (35-49 years old), while current tobacco users (n=6543) had the highest proportion in the middle age group (50-65 years old). Magnitude wise there remained many more current tobacco users compared to past 30-day e-cigarette users (Figure 5.3). Among female past 30-day e-cigarette users, the prevalence of COPD was 19.95%, while males had a prevalence of COPD of 10.40% (past 30-day e-cigarette users, n=404) (Figure 5.4). When examining dual smoking behaviour, females had higher rates of COPD in all groups compared to males; past 30-day e-cigarette and current tobacco use (19.93%, n=281 vs. 9.57%, n=282), past 30-day e-cigarette and former tobacco use (20.72%, n=111 vs. 12.82%, n=117), no past 30-day e-cigarette use and current tobacco use (13.26%, n=2873 vs. 8.82%, n=3107), no past 30-day e-cigarette use and former tobacco use (6.48%, n=8919 vs. 5.56%, n=9004) and no past 30-day e-cigarette use and never tobacco use (2.59%, n=8407 vs. 1.68%, n=4644) (Figure 5.5).

Table 5.1: Descriptive statistics of Canadian cohort aged 35 years or older (n=37,754)

Variable	Level	With COPD	Without COPD	Total (N)
Primary independent variable				
Past 30-Day E-Cigarette use	Yes	15.13%	84.88%	800
	No	5.49%	94.51%	36,954
Dual e-cigarette and tobacco use	Past 30-day e-cigarette user and current tobacco user	14.74%	85.26%	563
	Past 30-day e-cigarette user and former tobacco user	16.67%	83.33%	228
	Past 30-day e-cigarette user and never tobacco user	0.00%	100%	9
	No past 30-day e-cigarette use and current tobacco user	10.95%	89.05%	5980
	No past 30-day e-cigarette use and former tobacco user	6.02%	93.98%	17,923
	No past 30-day e-cigarette use and never tobacco user	2.27%	97.73%	13,051
Person-Level Factors				
Age	35-49	1.92%	98.08%	9981
	50-65	5.29%	94.71%	13,071
	65 or older	8.62%	91.38%	14,702
Sex	Female	6.10%	93.90%	20,595
	Male	5.22%	94.78%	17,159
Highest level of education	Post-secondary certificate diploma or university degree	4.32%	95.68%	23,303
	Secondary school graduation, no post-secondary education	6.05%	93.95%	8647
	Less than secondary school graduation	10.72%	89.28%	5804
Situational Factors				
Past 12-month alcohol consumption	Regular drinker	4.28%	95.72%	22,782
	Occasional drinker	6.99%	93.01%	6426
	Did not drink	8.52%	91.48%	8546
Exposure to environmental tobacco smoke	Yes	14.56%	85.44%	2727
	No	5.01%	94.99%	35,027
Product Factor				
Smoking status	Current	11.28%	88.72%	6543
	Former	6.15%	93.85%	18,151
	Never	2.27%	97.73%	13,060

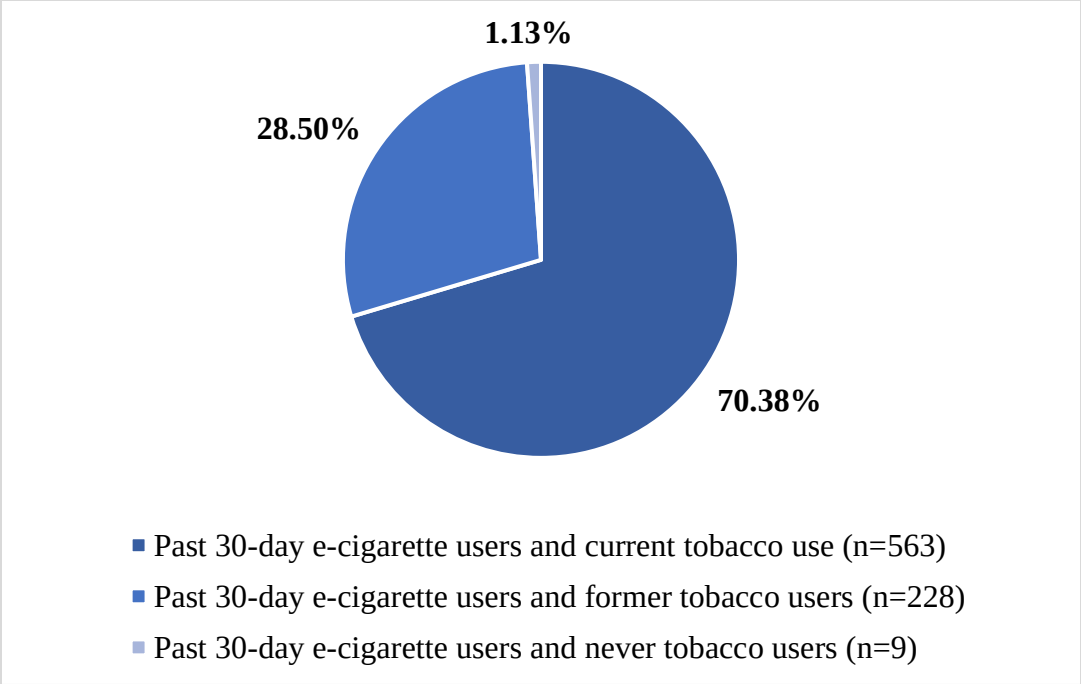

Figure 5.2: Pie chart showing the proportion of e-cigarette users by tobacco smoking status.

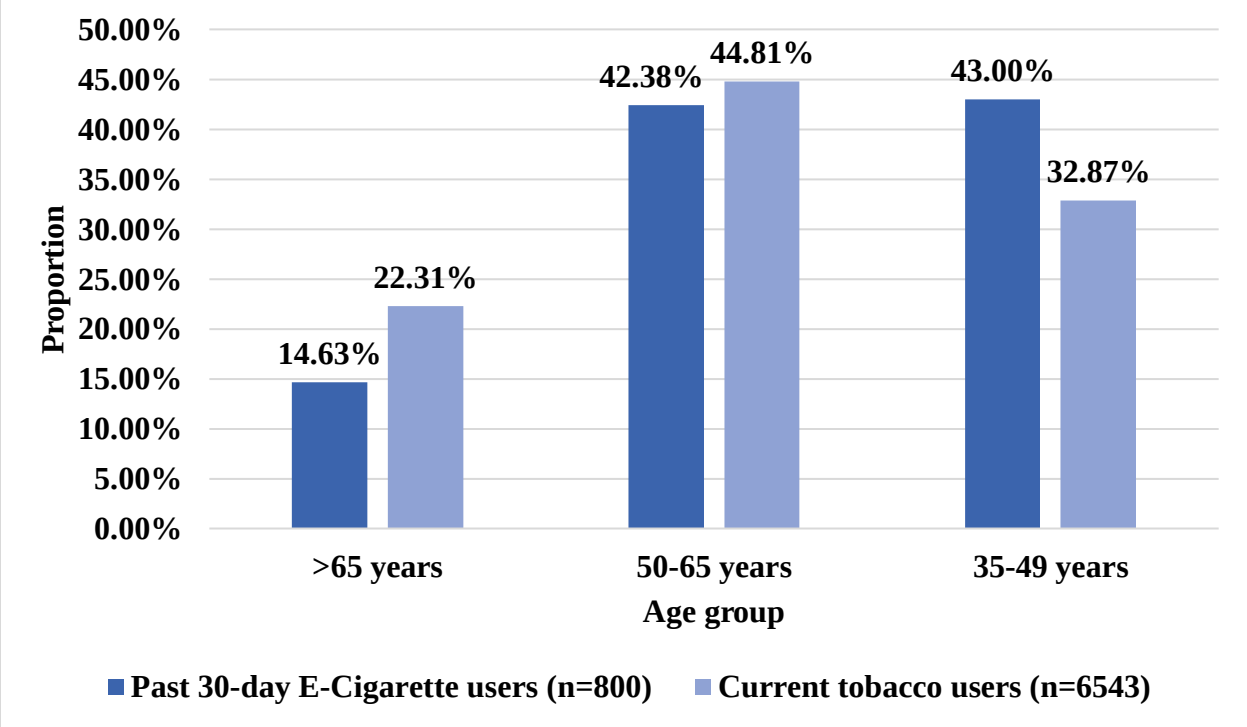

Figure 5.3: Bar chart depicting the proportion of past 30-day E-cigarette users and current tobacco smokers by age group.

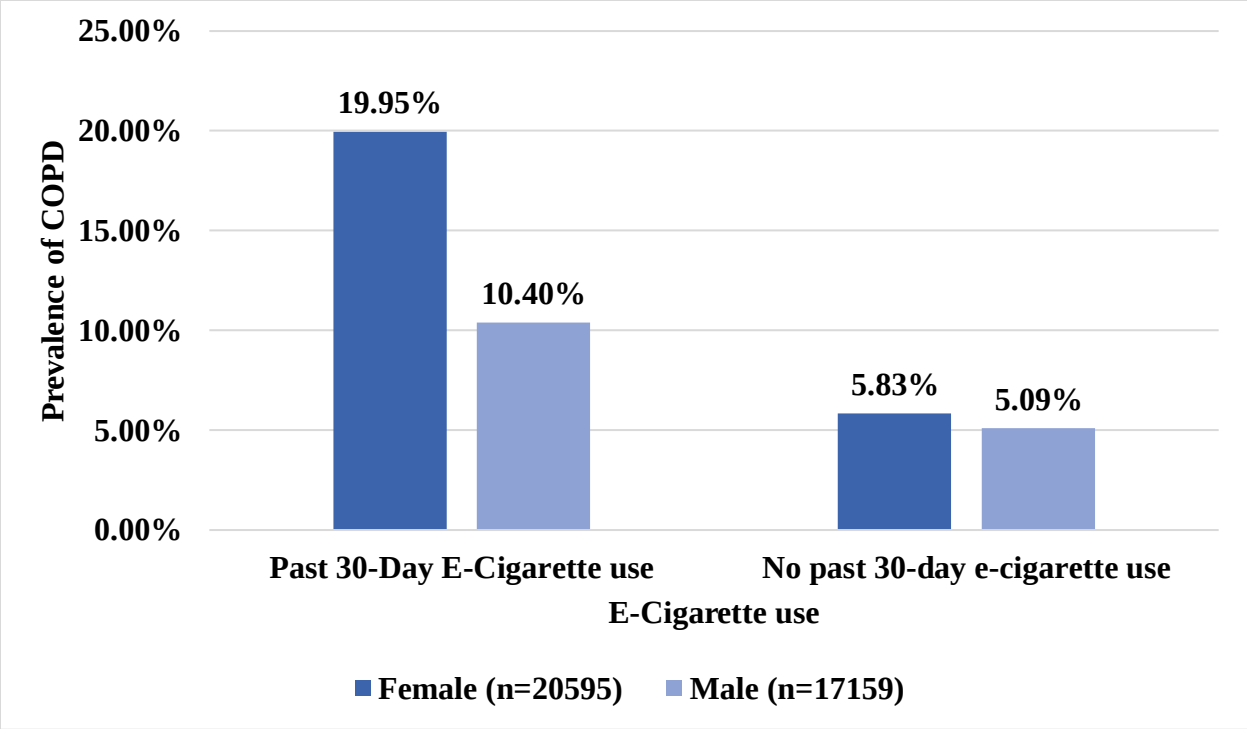

Figure 5.4: Bar chart depicting the prevalence of COPD by e-cigarette use among females and males.

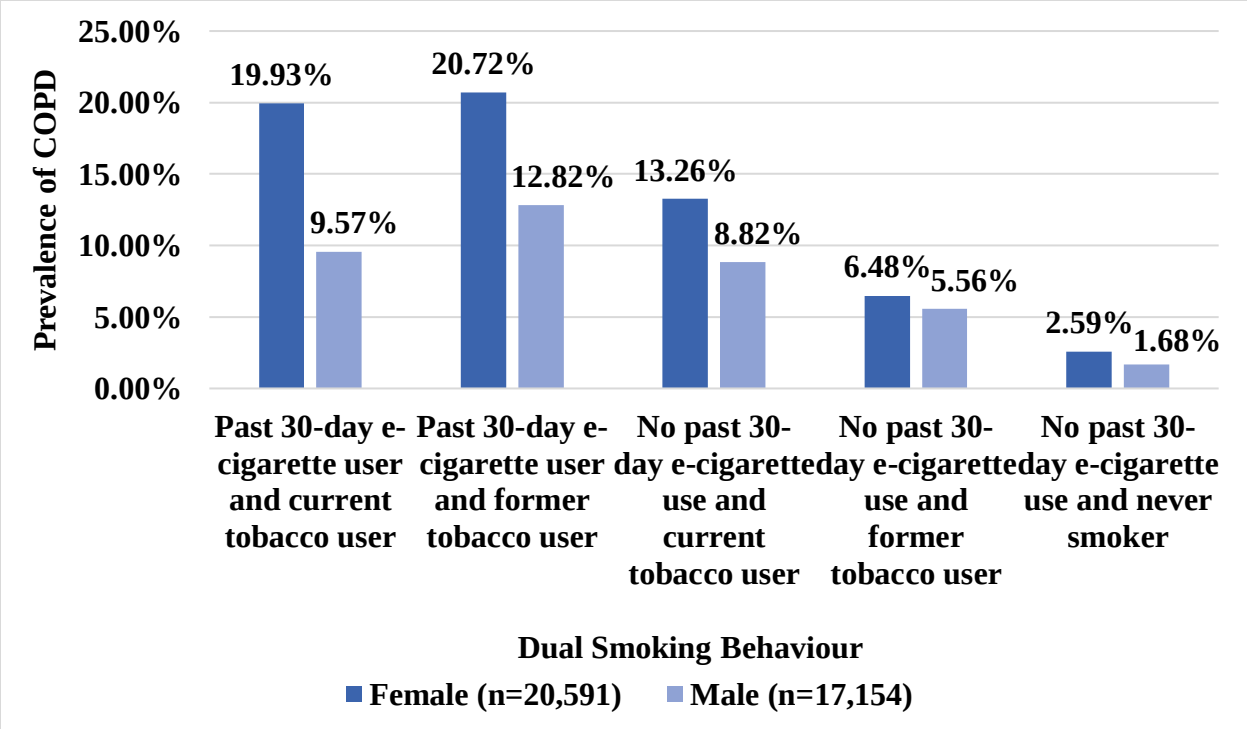

Figure 5.5: Bar chart depicting the prevalence of COPD by dual smoking behaviour among females and males.

5.3.2 Logistic regression analysis

The results of logistic regression analysis are detailed in Table 5.2.

The first part of the study (Models 1-3, Table 5.2) used past 30-day e-cigarette use as the primary independent variable. Canadians aged 35 years old or older who were past 30-day e-cigarette users were 3.4 times more likely (95% CI: 2.49-4.61) to report COPD compared to non past 30-day e-cigarette users (Model 1, crude association). A past 30-day e-cigarette and sex interaction term was significant (p-value < 0.05) in Model 2 and Model 3. When adjusted for age and smoking status (Model 2), the association between past 30-day e-cigarette use and COPD remained significant (Female aOR=2.96, 95% CI: 2.90-3.01; Male aOR=1.48, 95% CI: 1.45-1.52) (Figure 5.6). In the final model (Model 3, adjusted for age, smoking status, education, alcohol and environmental tobacco smoke), past 30-day e-cigarette users were more likely to report COPD compared to no past-30 day e-cigarette users (Female aOR=3.00, 95% CI: 2.95-3.05; Male aOR=1.47, 95% CI:1.43-1.50) (Figure 5.7). There was no evidence of multicollinearity (VIF ranged from 1.04-1.15) and the Hosmer Lemeshow test was used to assess model fit (p > 0.05).

When examining dual use of e-cigarettes and tobacco (Models 4-6, Table 5.2), it is important to note that 9 individuals reported e-cigarette use and never tobacco use. This subgroup was removed from the analysis leaving 5 groups (past 30-day e-cigarette users and current tobacco users, past 30-day e-cigarette users and former tobacco users, no past 30-day e-cigarette users and current tobacco users, no past 30-day e-cigarette users and former tobacco users and no past 30-day e-cigarette users and never tobacco users). The crude association between dual use and COPD status found that individuals who were both past 30-day e-cigarette and current tobacco users were 8.45 times more likely (95% CI: 5.63-12.66) to report having COPD compared to those with no past 30-day e-cigarette use and never tobacco smokers (Model 4). This association persisted when adjusting for age and sex in model 5 (aOR=13.65, 95% CI: 13.41-13.90) and in the final model (Model 6) when adjusting for age, sex, education, past 12 months alcohol use, and environmental tobacco smoke (aOR=14.16, 95% CI: 13.91-14.42).

Unlike models 1-3, there was not a statistically significant interaction between dual use and sex, however, females were more likely to report COPD compared to males in model 5 (aOR=1.54, 95% CI: 1.53-1.55) and model 6 (aOR=1.45, 95% CI: 1.44-1.46). There was no evidence of multicollinearity (VIF ranged from 1.03-1.16) and the Hosmer Lemeshow test was used to assess model fit ($p > 0.05$).

Table 5.2: Logistic Regression Analysis: Association between smoking behaviour (e-cigarette and dual use) with COPD status

Model	Primary independent variable		Odds Ratio (95% CI)	p-value
Primary Independent Variable: Past 30-day e-cigarette use				
Model 1[1] (Reference: No past 30-day e-cigarette use)	Past 30-day e-cigarette use		3.39 (2.49-4.61)	< 0.0001
Model 2[2] (Reference: No past 30-day e-cigarette use)	Past 30-day e-cigarette use | Sex Interaction	Females	2.96 (2.90-3.01)	< 0.0001
		Males	1.48 (1.45-1.52)	
Model 3[3] (Reference: No past 30-day e-cigarette use)	Past 30-day e-cigarette use | Sex Interaction	Females	3.00 (2.95-3.05)	< 0.0001
		Males	1.47 (1.43-1.50)	
Primary Independent Variable: Dual e-cigarette/tobacco use				
Model 4[4] (Reference: No past 30-day e-cigarette use and never tobacco smoker)	Past 30-day e-cigarette user and current tobacco user		8.45 (8.30-8.60)	< 0.0001
	Past 30-day e-cigarette user and former tobacco user		9.64 (9.42-9.87)	< 0.0001
	No past 30-day e-cigarette use and current tobacco user		6.50 (6.44-6.56)	< 0.0001
	No past 30-day e-cigarette use and former tobacco user		2.73 (2.70-2.75)	< 0.0001
Model 5[5] (Reference: No past 30-day e-cigarette use and never tobacco smoker)	Past 30-day e-cigarette user and current tobacco user		13.65 (13.41-13.90)	< 0.0001
	Past 30-day e-cigarette user and former tobacco user		15.50 (15.13-15.89)	< 0.0001
	No past 30-day e-cigarette use and current tobacco user		8.41 (8.33-8.49)	< 0.0001
	No past 30-day e-cigarette use and former tobacco user		2.60 (2.58-2.63)	< 0.0001
Model 6[6] (Reference: No past 30-day e-cigarette use and never tobacco smoker)	Past 30-day e-cigarette user and current tobacco user		14.16 (13.91-14.42)	< 0.0001
	Past 30-day e-cigarette user and former tobacco user		16.83 (16.41-17.25)	< 0.0001
	No past 30-day e-cigarette use and current tobacco user		8.55 (8.47-8.64)	< 0.0001
	No past 30-day e-cigarette use and former tobacco user		2.96 (2.93-2.99)	< 0.0001

[1]Crude association between past 30-day e-cigarette use and COPD
*[2]Past 30-day e-cigarette use*Sex interaction term and COPD (adjusted for age, and smoking status) reporting interaction term.*
*[3]Past 30-day e-cigarette use*Sex interaction term and COPD (adjusted for age, smoking status, education, alcohol, environmental tobacco smoke).*
[4]Crude association between dual use (past 30-day e-cigarette and tobacco smoking) on COPD.
[5]Dual use and COPD (adjusted for age and sex)
[6]Dual use and COPD (adjusted for age, sex, education, alcohol, environmental tobacco smoke)

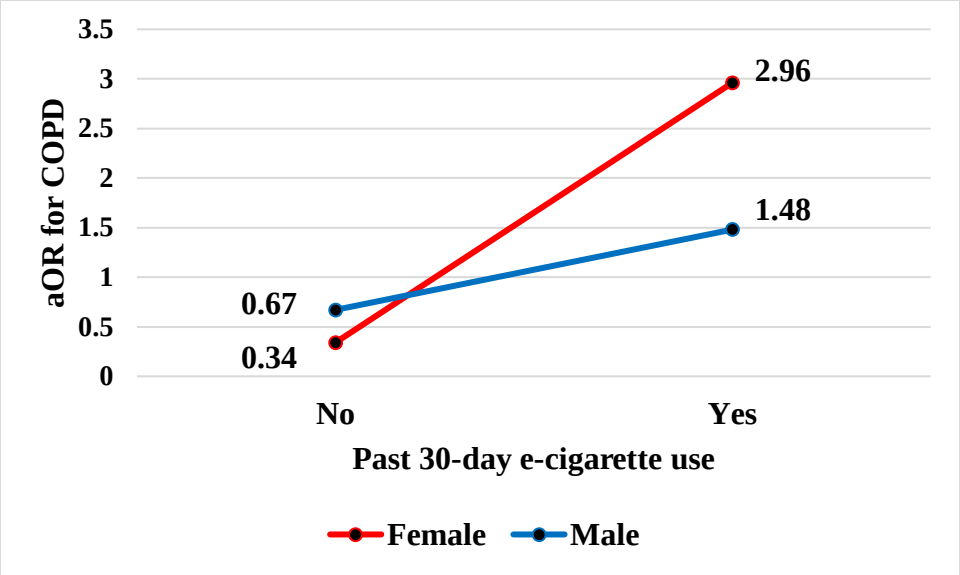

Figure 5.6: Interaction plot from Model 2 showing the association (adjusted odds ratio; aOR) between COPD status and the interaction between sex (female or male) and past 30-day e-cigarette use adjusted for age and smoking status.

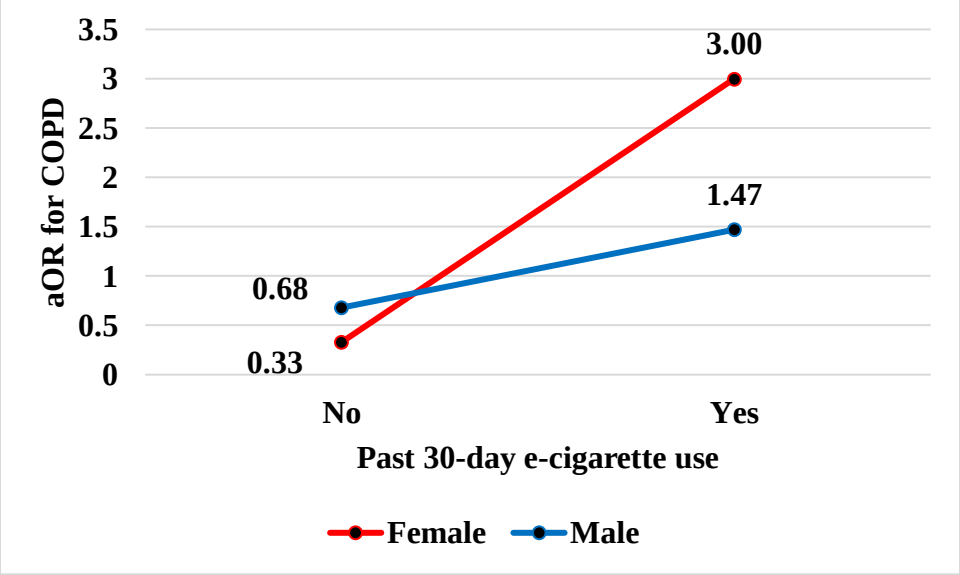

Figure 5.7: Interaction plot from Model 3 showing the association (aOR) between COPD status and the interaction between sex (female or male) and past 30-day e-cigarette use adjusted for age, smoking status, education, alcohol use and environmental tobacco smoke.

5.4 Discussion

This study is used Canadian data from Ontario, British Columbia, Nova Scotia and the Northwest Territories to examine the association between e-cigarette use and COPD. The overall prevalence of COPD in our sample of Canadians aged 35 years old and older was 5.70%, with past 30-day e-cigarette users having an almost three-fold increase, and dual users reporting an even higher prevalence of COPD (Table 5.1 and Figure 5.3). Our results indicate that past 30-day e-cigarette use among Canadians was independently associated with COPD, with dual users having higher odds of reporting COPD, which support findings from previous studies.[18,19,47,48] Furthermore, we identified an effect modification by sex (Table 2), which has not previously been reported and has potential ramifications due to sexual dimorphisms in nicotine metabolism, addiction, and the onset of negative health consequences such as COPD.

We found a higher prevalence of COPD among females compared to males and a stronger association between e-cigarette use and COPD among females (Table 5.1, Table 5.2). Previous studies reported similar results with the prevalence of COPD being higher among females compared to males.[18,19,48] However, they did not examine the association between e-cigarette use and sex on COPD status. In addition, contrary to existing literature, we found the female to male ratio of past 30-day e-cigarette users to be approximately 1:1 (n=396 females; n=404 males), with the ratio remaining similar between sexes for dual use. Sex-based differences in the onset of COPD as a result of tobacco use has been well characterized and discussed in the introduction with different mechanisms proposed (genetics, female sex hormone levels, cytokine expression, nicotine metabolism, and lower threshold of exposure).[24,28-30] As e-cigarettes are a type of electronic nicotine delivery system, it is reasonable to assume some crossover in the pathogenesis of COPD between e-cigarette and conventional tobacco use hence, resulting in similar outcomes in females when compared to males. Our findings are relevant as e-cigarette use leads to nicotine dependence,[13,16] with one study concluding that quitting e-cigarettes was more difficult than conventional tobacco[49] however, there is a lack of consensus on the matter as other studies have suggested e-cigarettes do not have the addictive potential of conventional tobacco cigarettes,[50,51] requiring more research. Irrespective of the magnitude of addiction, nicotine is known to be addictive, and females may be more responsive to social influences and vulnerable to targeted marketing especially those incorporating self-image, weight control and

health.[50] Females have quicker nicotine and cotinine metabolism due to estrogen, which worsens cessation efforts in tobacco research,[51] and develop symptoms of COPD at lower levels of tobacco exposure compared to males.[24,28,29] One study examining US e-cigarette sales found the majority of e-cigarette sales between 2013-2018 were for nicotine containing products, and non-nicotine products accounted for less than 1% of the market share.[52] While data from the 2017 Canadian Tobacco, Alcohol and Drugs survey (CTADS) found most ever e-cigarette users surveyed (78.9% of males and 70.1% of females) used nicotine the last time they vaped[10] further illustrating that it is essential to investigate and inform of potential deleterious effects of e-cigarettes such as COPD and to account for potential sex-based differences.

Dual use of conventional tobacco and e-cigarettes is an emerging public health concern. This study found the majority of past 30-day e-cigarette users were also current (past 30-day) tobacco users and had a stronger association with COPD compared to current tobacco only users. Due to sampling limitations, we were unable to assess the association between past 30-day e-cigarette use and COPD among never tobacco users, though, previous studies identified an association exists.[40,47,48] In previous studies, the majority of conventional smokers reported using e-cigarettes to aid in tobacco cessation, harm reduction and for its taste.[53,54] There is a lack of consensus in the published literature of the efficacy of e-cigarettes as tobacco cessation devices with a recent systematic review and meta-analysis concluding that individuals using e-cigarettes had 28% lower odds of quitting conventional tobacco cigarettes compared to non e-cigarette users.[55] Furthermore, dual use with e-cigarettes may circumvent existing smoke-free policies which are shown to motivate and support tobacco cessation,[54] reduce individuals perceptions to quit[56,] and increase the dosage of nicotine throughout the day, thus inhibiting smoking cessation by increasing nicotine addiction. The latter was shown in a study conducted in France, which found that dual users were exposed to more nicotine throughout the day compared to only e-cigarette users; however, they did not compare their results with conventional tobacco use.[57] Our results showed that a significant proportion of past 30-day e-cigarette users were former conventional tobacco smokers. As our results are cross-sectional, it is not possible to ascertain whether e-cigarette use, or COPD occurred initially. Therefore, “switching” from conventional tobacco use to e-cigarette use as a harm reduction strategy may influence the strength of the association between dual use and COPD. There is evidence indicating that current or former conventional tobacco smokers with COPD are more likely to try e-cigarettes compared to conventional

tobacco smokers without COPD[58] for tobacco cessation or reduction. However, this change in nicotine product may prevent conventional tobacco smoking or it may lead to re-uptake of tobacco cigarettes as e-cigarettes do not replicate the conventional tobacco experience.[56] A longitudinal study in the USA found that former tobacco smokers who used e-cigarettes to quit smoking were more likely to relapse.[59] In contrast, those who used e-cigarettes due to the flavors and smells were less likely to return to conventional tobacco smoking.[59] The potential for additive or synergistic health outcomes due to dual e-cigarette and conventional tobacco use on the severity of COPD requires additional research. An American cross-sectional study using the Heart eHealth Study found dual users compared to conventional tobacco users exhibited worse median general health scores and breathing scores, including COPD.[60] While an observational study concluded that dual users were more nicotine dependent, inhaling more nicotine compared to conventional tobacco only smokers, found no statistically significant difference in the number of tobacco cigarettes smoked and found no evidence supporting using e-cigarettes as a harm reduction strategy among current smokers.[41] In contrast to this result, an Italian retrospective cohort study (n=44) with a three year follow up compared the exacerbation rate of COPD between dual users, e-cigarette only users and single users of tobacco.[61] They observed a significant reduction in COPD exacerbation rate among e-cigarette only and dual users but no significant change among tobacco smokers.[61] Additionally, they reported complete tobacco cessation in around 60% of the dual users by the third follow up visit, and a significant reduction in cigarettes smoked in 40% of the remaining dual users.[61] Therefore, the reduction in COPD exacerbation rates could be attributed to tobacco reduction or cessation but there was no improvement in lung function attributable to switching to e-cigarettes or dual use. The lack of consensus in the literature regarding e-cigarettes as harm reduction devices for COPD patients warrant further study to elucidate their therapeutic potential.

Study's strengths and limitations

This study had several strengths, including a large sample size using Canadian data to examine the association between e-cigarettes and COPD, and the dual use of e-cigarettes and conventional tobacco with COPD. We identified biological sex as an effects modifier in this association in our analysis, which has not been previously reported but is plausible based on previous research into COPD. However, due to societal and environmental factors influencing COPD we were unable

to examine gender differences or disentangle sex and gender-based differences. As our study is cross-sectional, we are unable to infer causality as we do not have a temporal component, we can only report potential association. It is possible individuals with COPD started using e-cigarettes or vice-versa. However, our findings are consistent with previous research. Furthermore, due to sample size limitations, we were unable to assess the association between past 30-day e-cigarette use among never conventional tobacco smokers with COPD. Another limitation of this study is the inability to assess nicotine levels and exposure frequency to e-cigarettes. As this was an exploratory, cross-sectional study, it is important to note that COPD is a chronic disease taking years to develop, e-cigarettes on the other hand a relatively new product, therefore this may have affected our estimates and limited the data available to us. The CCHS uses a complex sampling procedure to provide reliable health region level estimates but there is potentially an issue due to clustering, however we incorporated the weights provided in our analysis to better represent the population under study. There is a need to develop validated, comprehensive methods to assess e-cigarette usage similar to conventional tobacco smoking (pack years, classification such as never smokers, experimental smokers, former smokers, occasional, daily and current smokers) examining nicotine content, type of device and the dosage and frequency of exposure to improve estimates. Finally, our e-cigarette variable was past 30-day e-cigarette use, a binary yes or no question. As such, ever users of e-cigarettes who did not use e-cigarettes in the past 30-days would respond no. This may result in over or under-estimation of the association between e-cigarette use and COPD. However, previous studies have indicated that ever e-cigarette use is associated with future current tobacco use, potentially leading to COPD.[62-67] Future studies should incorporate past 30-day, ever and never e-cigarette use where possible.

5.5 Conclusion

This study uses Canadian data from three provinces and one territory, examining the association between e-cigarettes and dual tobacco and e-cigarette use and COPD. Our findings indicate that there is an independent association between e-cigarette use and COPD that is more pronounced among females but is also present in males. While the majority of tobacco smokers who use e-cigarettes report it is for tobacco cessation, the majority of past 30-day e-cigarette users were dual users. Increased efforts need to be made in policy and health promotion campaigns to better inform individuals on the risks associated with e-cigarette use as current norms and beliefs have been shaped by e-cigarette marketing strategies and individuals are not aware of the potential harms related to e-cigarette use. Further longitudinal studies are required to assess whether e-cigarette use among never conventional tobacco smokers can lead to the development of COPD and whether e-cigarette use among COPD patients can lead to a decrease in the severity of the disease.

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CHAPTER 6: E-CIGARETTES AS TOBACCO INITIATION DEVICES: A SYSTEMATIC REVIEW AND META-ANALYSIS[4]

Introduction: E-cigarettes are electronic nicotine delivery systems being rapidly adapted by youth as conventional tobacco initiation decreases, partially attributed to effective policies and initiatives. The gateway hypothesis posits that e-cigarettes can lead to tobacco initiation. The purpose of this study is to examine if e-cigarette use among naïve nicotine users leads to conventional tobacco use over time.

Methods: The following databases were searched: PubMed, Ovid MEDLINE, Public Health Database, Scopus and Cochrane Library. Inclusion criteria included: 1) human participants; 2) open access, peer-reviewed English language studies published between 2010-2019; 5) longitudinal studies; 6) baseline never smokers; 7) baseline e-cigarette use assessed; 8) conventional tobacco initiation assessed at follow-up; and 9) control group of nicotine naïve participants (never e-cigarette and conventional tobacco users). Risk of bias was assessed within and between studies. Random effects models were used for meta-analysis.

Results: Out of the 3412 articles identified, 17 were used in quantitative synthesis (meta-analysis); 16 of the 17 examined the association of ever e-cigarette use at baseline and tobacco initiation at follow up and 7 or the 17 examined the association of ever e-cigarette use at baseline and current tobacco use at follow up. Ever e-cigarettes users were aOR=3.28 times more likely (95% CI: 2.74-3.92; I^2=62.91) to initiate conventional tobacco smoking at follow-up and aOR=1.89 (95% CI: 1.34-2.66; Q=28.43) times more likely to be current tobacco smokers at follow up.

Conclusions: This study provides up to date data showing that e-cigarette use is associated with tobacco initiation over time, providing up to date evidence to public health professionals and policymakers based on longitudinal studies that can inform planning, evaluation and implementation of comprehensive tobacco prevention and control programs.

Keywords: E-cigarettes, tobacco smoking, initiation, gateway hypothesis

[4] **Mahmood R**. et. al. E-cigarettes as tobacco initiation devices: A systematic review and meta-analysis. Manuscript under preparation for submission.

6.1 Introduction

The e-cigarette is modern battery-powered electronic nicotine delivery system (ENDS) which functions by vaporizing a liquid solution (e-liquid) containing nicotine (can be no nicotine to higher levels), flavours, and other additives (i.e. propylene glycol and vegetable glycerin).[1,2] E-cigarettes have different designs, generations and appearance but are similar in operation and consist of common components such as an e-liquid containing cartridge and an atomizer to heat the e-liquid.[1] Once the e-liquid is heated sufficiently to create an aerosolized vapour the user inhales the vapour through the mouthpiece.[1] The aerosols give the users a somewhat similar experience to conventional tobacco smoking although former smokers may feel that e-cigarettes are not necessarily reflective of the conventional tobacco smoking lived experience.[3] E-cigarettes were developed by a Chinese pharmacist in 2003, patented internationally in 2007 and have since been increasingly adopted globally.[2]

E-cigarette uptake has rapidly risen, especially among youth and young adults. In the United States of America between 2011-2018, past 30-day e-cigarette use has risen from 1.5% to 20.8% among high school students.[4] In response to the explosive growth of e-cigarette use, surpassing even conventional tobacco cigarette use in 2014 among youth, the US Surgeon General concluded that e-cigarette use is a significant public health concern.[1] In Canada, e-cigarette uptake has not been as pronounced as in the USA with the Canadian Student Tobacco, Alcohol and Drugs Survey (CSTADS) reporting the prevalence of past 30-day e-cigarette use among students in grades 7-12 to have risen from 6.5% in 2014/15 to 10.0% in 2016/17.[5] Concurrently with the rise in e-cigarette use, there has been an overall decline in conventional tobacco use in Canada, however, there was a statistically significant increase in past 30-day tobacco use from 13% (2015) to 15% (2017).[6]

Annual e-cigarette sales in the United states have grown rapidly from a modest $76 million USD in 2011 to approximately $1.3 billion USD in 2017.[7] There are different modalities contributing to e-cigarette uptake including successful targeted advertising campaigns through digital marketing, social media, television, radio, print and retail establishments,[8,9] acceptability,[10-12] easy accessibility,[13,14] perceived safety,[9,11-13,15-17] aesthetically pleasing,[12,13,16,18] perceptions of lack of addictivity,[19] perceptions of being a tobacco cessation device,[15,17] varied flavours appealing to youth and adults[16,12] and currently being in vogue leading to societal pressure.[9,16,18]

The rise in e-cigarette use raises concerns regarding long-term public health consequences. Due to the relatively recent introduction of e-cigarettes and the rapid uptake, studies examining health consequences are lagging with a lot of unknown and uncharacterized direct health effects and indirect effects such as consequences of nicotine addiction and the potential for e-cigarettes to be a gateway to future tobacco initiation. Proponents of e-cigarettes suggest that it can be used as a harm reduction device leading to a reduction in conventional smoking[20-24] however, there is a lack of consensus with other studies suggesting e-cigarettes are not an effective tobacco cessation device, and might make tobacco cessation more difficult.[25-27] Moreover, there is a growing body of evidence that has shown there is an association between e-cigarette use and subsequent smoking initiation among never-smoking adolescents and young adults. Results from several early cross-sectional studies found an association between e-cigarette use and conventional tobacco initiation.[28] However, these findings were limited as several confounding factors, including age groups and geographic location were not considered.[28] Furthermore, a recent longitudinal study had similar results (e-cigarette use leads to tobacco initiation) and they assessed this association using validated tobacco initiation susceptibility measures, classifying never smokers as susceptible (high risk) and non-susceptible (low risk) to tobacco use, with baseline e-cigarette users in both groups having higher odds of initiation compared to non e-cigarette users.[29]

The gateway hypothesis was initially used when examining if conventional tobacco use led to illegal drugs, this has since been applied to the relationship between tobacco naïve individuals who initially start using e-cigarettes and eventually start conventional tobacco use.[30] Two major criticisms of this hypothesis are there is no causal explanation of why tobacco and e-cigarette naïve individuals start with e-cigarettes rather than conventional tobacco and why e-cigarette users eventually transition to conventional tobacco use or dual use.[30] To address the first criticism, the flavour, health, role model, concealment and acceptance hypotheses have been proposed to explain why tobacco and e-cigarette naïve individuals are more likely to start with e-cigarettes compared to conventional tobacco, while the addiction, accessibility and experience hypotheses address the latter criticism.[30] A simpler argument against the gateway hypothesis is that while e-cigarette use is increasing among youth, why are tobacco rates decreasing.[31] While lower tobacco use among youth is a trend seen in many countries, making the aforementioned assumption is applying aggregate population level observations to individuals; the ecological

fallacy and only well designed prospective cohort or randomized clinical trials can truly assess the gateway hypothesis.[31]

After examining the literature it is clear there is a lack of consensus on the gateway hypothesis, but there is proposed relationship between e-cigarette use and tobacco initiation which may negatively impact effective tobacco control policies and societal and community efforts to reduce the incidence and prevalence of tobacco use, thus, reducing the associated morbidity and mortality associated with tobacco use. This could lead to a delayed onset neo-tobacco epidemic if not appropriately investigated. The purpose of this study was to 1. Determine if e-cigarette use increases the risk of conventional tobacco initiation among a cohort of never conventional tobacco users; 2. Examine whether different e-cigarette use behaviors (past 30-day, ever use) affect conventional tobacco use; and 3. Evaluate what if any sex differences exist in conventional tobacco initiation after e-cigarette use.

6.2 Materials and Methods

6.2.1 Eligibility criteria

Studies that were eligible included study participants of any age that were never conventional tobacco smokers at the start of the study (population). These studies assessed e-cigarette use in the study population (intervention), included non-e-cigarette users and never conventional tobacco smokers as the control group (comparator) and measured conventional tobacco initiation (outcome). English language, peer-reviewed, open access, longitudinal prospective or randomized cluster studies published since 2010 were included in this study.

6.2.2 Information sources

Studies were identified through searching electronic databases and snowballing from reference lists of the included studies. This search was applied to the PubMed, MEDLINE: Ovid MEDLINE, Public Health Database, Scopus and Cochrane Library databases. The last search was run on February 3rd, 2020.

6.2.3 Search

Our search strategy included using medical subject headings and keywords applied to the databases searched as appropriate. The search strategy was arranged by e-cigarette use and conventional tobacco smoking initiation. The PubMed search used in this study was the following: ((("electronic cigarettes") OR "e cigarettes")) AND ((((("initiation") OR "smoking initiation") OR "gateway") OR "tobacco use")

6.2.4 Study selection

Articles included were screened in two steps: 1) title and abstract screening and 2) full-text screening. Initial calibration was conducted by two authors using 20 randomly selected articles. Results were compared and discussed with the third author, after which eligibility criteria were refined followed by dual independent screening. In the case of disagreement after screening (title and abstract or full-text screening), the two authors would discuss the article among themselves and in cases where consensus was not achieved, a third author would provide the tie-breaker vote. Articles which satisfied the following criteria were included: 1) human participants, 2) published between 2010-2020, 3) English language, 4) open access or accessible through the

University of Saskatchewan Library, peer-reviewed articles, 5) longitudinal studies, 6) initial population of never smokers quantified at baseline, 7) quantified e-cigarette use among cohort at baseline, 8) quantified conventional tobacco initiation at follow-up, 9) had a control group of nicotine naïve participants (never e-cigarette and conventional tobacco users).

6.2.5 Data collection and items

Data extraction used Microsoft Excel sheets developed by the authors of the study and dual extraction was employed. After completing data extraction, the two authors compared results with a third providing a tie-breaker vote in case of disagreement. Information extracted from the included articles included: authors, year of publication, study design, the name of the study cohort (when applicable), type of intervention (school based or population based), country of the study, years the study was ongoing, follow up time in years, overall sample size, the age (mean, median or range) or grade of the population, definition of the intervention (ever e-cigarette use or past 30-day e-cigarette use), definition of the control group (never e-cigarette user, never conventional tobacco smoker or no past 30-day e-cigarette use, never conventional tobacco smoker), the sample size of the intervention and control group, type of outcome variable (tobacco initiation and current tobacco user) and quantitative data of the outcome variable (odds ratio, 95% confidence interval and risk ratio, 95% confidence interval). If multiple outcomes were presented, the most adjusted values were extracted to provide the most conservative estimates.

6.2.6 Risk of bias in individual studies

A modified Newcastle Ottawa Scale (NOS) for cohort studies[32] was used to assess the risk of bias. Two authors independently assessed bias in the selection, comparability and outcome of each study, after which results were compared. The authors discussed any disagreement and in cases where consensus was not reached a tiebreaker was provided by the third author (See Appendix 1 for modified NOS Scale and grading).

6.2.7 Summary measures and synthesis of results

The majority of articles assessing tobacco initiation reported odds ratio (OR) and 95% confidence intervals (95% CI) as the outcome measure over time. Hence, the meta-analysis was conducted by computing and/or incorporating the odds ratio from the studies included using

random effects models. Random effects models were used to provide conservative estimates of the pooled data, with wider confidence intervals compared to fixed effects models.[33] Furthermore, while the fixed effects model assumes the true effect size is the same in all studies, the random effects model is more appropriate for this study as it assumes the summary measure varies from study to study and the result is the mean of these effects[34] and it accounts for both within-study and between-study variability.[35] The I^2 statistic describes the total variation between studies due to heterogeneity rather than chance and is calculated as $I^2=100\%*(Q-df)/Q$; where Q is the Cochrane heterogeneity statistic and df is degrees of freedom.[36] Broadly, I^2 can be categorized as low (25%), moderate (50%) and high (75%), though the methodological and clinical implications of potential heterogeneity should be accounted for when conducting a meta-analysis.[36] Studies were combined based on baseline ever e-cigarette use (and never conventional tobacco smokers) and at follow-up both tobacco initiation (first time smokers, not necessarily past 30-day tobacco smokers) and current tobacco smokers (individuals who smoked conventional tobacco cigarettes over the past 30-days who were new tobacco initiators).

6.2.8 Risk of bias across studies

In order to assess how risk of selection bias might affect the results of the meta-analysis, publication bias was assessed using both funnel plots and Egger's test. The funnel plot has the standard error on the y-axis and log odds ratio on the x-axis. More precise estimates of the intervention effect appear higher on the funnel plot while smaller less precise estimates scatter at the bottom of the plot. If they are symmetrical it suggests an absence of bias, but if there is a skew or asymmetry it suggests potential publication bias.[37] Furthermore, Egger's test, a form of linear regression of the normalized effect estimate against precision was used to confirm the presence of potential publication bias.[37]

6.2.9 Additional analysis

In cases where publication bias was detected, the Duval and Tweedie's trim and fill was conducted to correct funnel plot asymmetry. This non-parametric methodology is a simple estimation approach where the asymmetric outlying part of the funnel is trimmed, the symmetric remainder is used to estimate the centre of the funnel and the trimmed studies and their missing counterparts are returned (filled).[38] Due to the differences in follow-up time between studies, subgroup analysis was conducted to examine whether outcomes differed between studies based on follow-up time. We were unable to assess past 30-day e-cigarette use or sex-based differences in e-cigarette use and tobacco initiation as there were insufficient studies examining past 30-day e-cigarette use and no studies stratifying conventional tobacco initiation by sex.

6.3 Results

6.3.1 Study selection

In total, 3412 studies were identified through the database searches. After removing duplicates (n=1172), 2240 studies remained for title and abstract screening of which 2143 were excluded according to the eligibility criteria. After full-text screening (n=97), 73 articles were excluded with 24 articles remaining for qualitative synthesis[28,29,39-60] and 17 articles for quantitative synthesis (meta-analysis).[28,39-44,46,48,49,51,54-57,59,60] Studies excluded from meta-analysis was due to: 1) Did not assess baseline ever e-cigarette use, just past 30-day e-cigarette use;[29,45,52] 2) Did not provide the follow-up time;[47] 3) Outcome was risk ratios;[50,53] and 4) Assessed baseline e-cigarette use by nicotine vs. no nicotine content.[58]

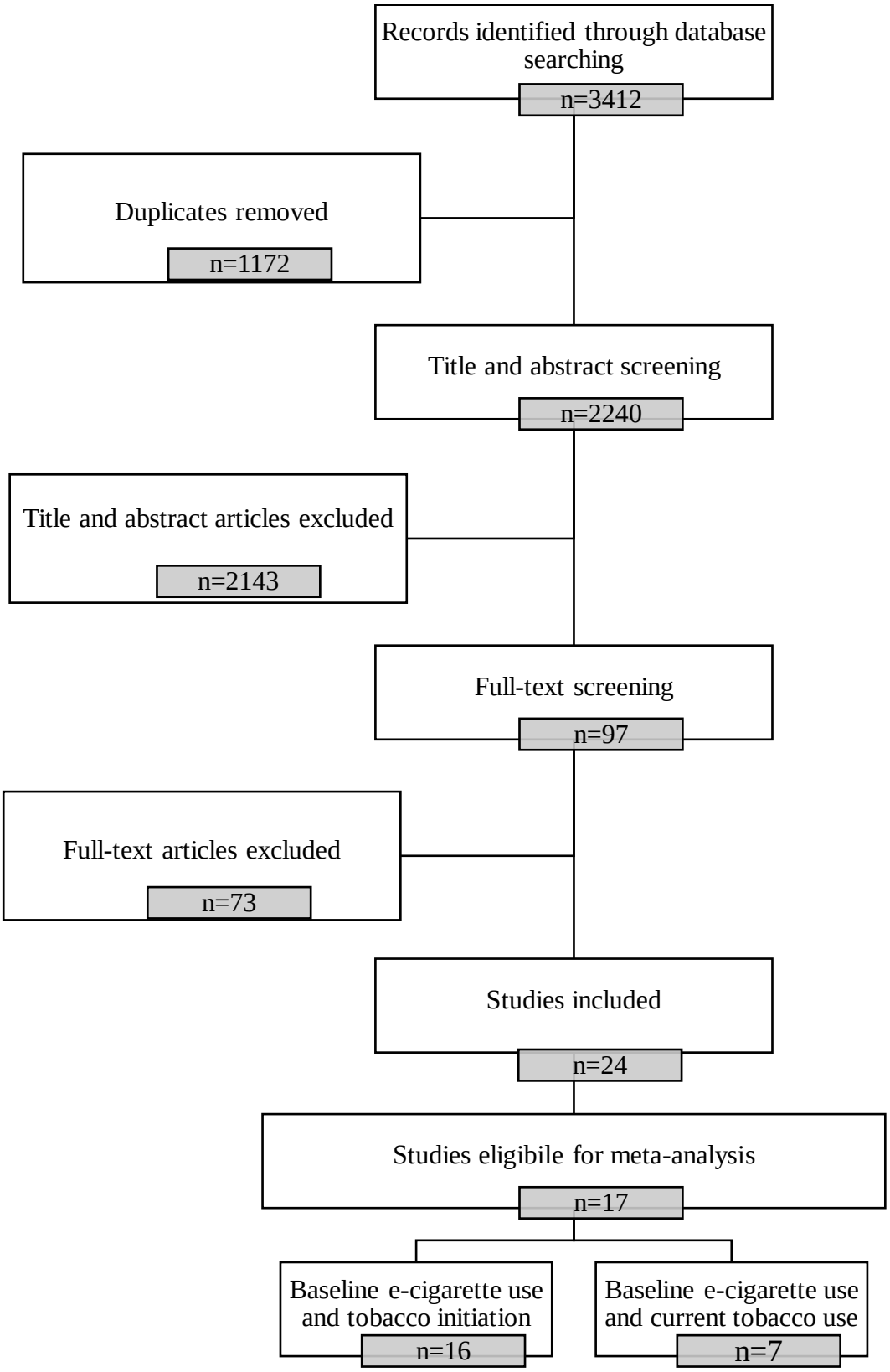

Figure 6.1: PRISMA Flow Diagram detailing study selection

6.3.2 Study characteristics

There were 24 final articles included in this study for qualitative synthesis. Characteristics of the studies from which data was extracted included longitudinal studies, either prospective cohort studies or prospective cluster randomized studies. The studies were published between 2015-2019 with the range of data collection from 2012-2016. The follow-up period of the interventions was between six months to two years. Studies included were from the United States of America (n=13), Canada (n=2), Mexico (n=1), United Kingdom (n=3), Germany (n=1), Netherlands (n=1), Finland (n=1), Romania (n=1) and China (n=1). Participants ranged from youth aged 11-13 years old to adults aged 35 and older based on the study. The majority of the studies assessed ever e-cigarette use as the intervention group with never e-cigarette and conventional tobacco smoking as the control group at baseline. The outcome of interest in the studies was either the initiation (ever use) of conventional tobacco smoking or current (past 30-day) conventional tobacco smoking at follow-up (Table 6.1).

Table 6.1: Summary of included study characteristics

Source	Study Design and Setting	Name of Study	Country	Follow up time (years) and years of study	Sample size	Factor under study	Control	Outcome variable	Outcome value	Covariables adjusted for in models (outcome value)
Aleyan, 2018[29]	Prospective Cohort School-based	COMPASS	Canada	2 2013/14-2015/16	9501	Past 30-day e-cigarette use (Baseline)	No Past 30-day E-Cigarette use, never smokers by smoking susceptibility	Tobacco initiation (Susceptible)	OR: 2.78 (95% CI: 1.84-4.20)	Sex, grade, ethnicity, friends who smoke cigarettes at baseline, weekly spending money, school
								Tobacco initiation (non-susceptible)	OR: 5.28 (95% CI: 2.81-9.94)	
Barrington, 2016[28]	Prospective Cohort School-based	Children's health Study	USA	1.5 2014-2016	298	Ever e-cigarette use (Baseline)	Never e-cigarette, never tobacco users	Tobacco initiation	OR: 4.29 (95% CI: 1.84-10.0)	sex, ethnicity, grade, parental education
Barrington, 2018[39]	Prospective Cohort School-based	Children's health Study Happiness & Health Study Yale Adolescent Survey Study	USA	1 2013-2016	6258	Ever e-cigarette use (baseline)	Never e-cigarette, never tobacco users	Tobacco initiation	OR: 4.57 (95% CI: 3.56-5.87)	sex, ethnicity, grade, study group
								Current tobacco smoker	OR: 3.51 (95% CI: 1.97-6.24)	

Berry, 2019[40]	Prospective Cohort Population based	Population Assessment of Tobacco and Health Study (PATH)	USA	2 2013-2016	6123	Ever e-cigarette use (Baseline)	Never e-cigarette, never tobacco users	Tobacco initiation	OR: 4.09 (95% CI: 2.97-5.63),	sex, age, ethnicity, parental education, urban/rural, living with tobacco user, noticing tobacco warnings, tobacco advertisement receptivity, nine measures of susceptibility/risk
								Current tobacco smoker	OR: 2.75 (95% CI: 1.60-4.73)	
Chien, 2019[41]	Prospective Cohort School-based	Taiwan Adolescent to Adult Longitudinal Study (TAALS)	Taiwan/China	2 2014-2016	12954	Ever e-cigarette use (Baseline)	Never e-cigarette, never tobacco users	Tobacco initiation	OR: 2.14 (95% CI: 1.66-2.75)	smoking susceptibility, father's education, mother's ethnicity, socioeconomic status, age, peer support
Conner, 2018[42]	Cluster-based randomized control trial School-based	Study reference 12–0155 (Faculty of Medicine, Leeds)	UK	1 2014-2015	1726	Ever e-cigarette use (Baseline)	Never e-cigarette, never tobacco users	Tobacco initiation	OR: 4.06 (95% CI: 2.94-5.60)	friend smokers, sex, family smokers, intentions, attitudes, norms, perceived behavioural control, self-efficacy, free school meals
Conner, 2019[43]	Cluster-based randomized control trial School-based	Study reference 12–0155 (Faculty of Medicine, Leeds)	UK	2 2014-2016	3994	Ever e-cigarette use (Baseline)	Never e-cigarette, never tobacco users	Tobacco initiation	OR: 2.78 (95% CI: 2.20-3.51)	Sex, ethnicity, SES, free school meals, friend smokers, family smokers, impulsivity, intentions, attitude, perceived norms, perceived behavioural control, self-efficacy
								Current tobacco smoker	OR: 1.27 (95% CI: 1.17-1.39)	

East, 2018[44]	Prospective Cohort Population-based	2016 Action on Smoking and Health Great Britain Youth longitudinal survey	UK	0.5 2016	923	Ever e-cigarette use (Baseline)	Never e-cigarette, never tobacco users	Tobacco initiation	OR: 10.57 (95% CI: 3.33-33.50)	Age, sex, school performance, problematic behaviours, alcohol use, smoking susceptibility, friends who smoke friends who vape, parents who smoke, parents who vape, sibling smokers, sibling vapers, public approve of smoking, public approve of e-cigarettes
Hammond, 2017[45]	Prospective Cohort School-based	COMPASS	Canada	1 2013/14-2014/15	17318	Past 30-day e-cigarette use (Baseline)	No Past 30-day E-Cigarette use, never smokers	Tobacco initiation	OR: 2.12 (95% CI: 1.28-1.62)	Age, sex, ethnicity, spending money, smoking status
Kinnunen, 2019[46]	Prospective Cohort School-based	Metropolitan Longitudinal Finland	Finland	2 2014-2016	1923	Ever e-cigarette use (Baseline)	Never e-cigarette, never tobacco users	Current tobacco smoker	OR: 2.92 (95% CI: 1.09-7.85)	Sex, Parent's education (SES), Other tobacco use
Kintz, 2019[47]	Prospective Cohort School-based	Children's Health Survey	USA	0.5-1 2014-2016	1293	Ever e-cigarette use (Baseline)	Never e-cigarette, never tobacco users	Tobacco initiation	OR: 4.91 (95% CI: 3.42-7.05)	Unadjusted, crude OR

Leventhal, 2015[48]	Prospective Cohort School-based		USA	0.5 2013-2014	2530	Ever e-cigarette use (Baseline)	Never e-cigarette, never tobacco users	Tobacco initiation	OR: 1.75 (95% CI: 1.10-2.77)	Age, sex, ethnicity, parental education, family structure, family smoking, peer smoking, mental health disorders, smoking susceptibility
Loukas, 2018[49]	Prospective Cohort College-based	Marketing and Promotions across Colleges in Texas project	USA	1.5 2014-2016	2558	Ever e-cigarette use (Baseline)	Never e-cigarette, never tobacco users	Tobacco initiation	OR: 2.26 (95% CI: 1.35-3.76)	Sex, age, ethnicity, school type, cigarette use susceptibility, family tobacco use, friend tobacco use,
Lozano, 2017[50]	Prospective Cohort School-based		Mexico	1.67 2015-2016	4695	Ever e-cigarette use (Baseline)	Never e-cigarette, never tobacco users	Tobacco initiation	aRR: 1.40 (95% CI: 1.22-1.60)	sex, age, parent SES, sensation seeking, friends that smoke, parents that smoke, siblings that smoke, tried alcohol, binge drinking and internet tobacco product advertising
								Current tobacco smoker	aRR: 1.43 (95% CI: 0.94-2.16)	

MacMillen, 2019[51]	Prospective Cohort Population-based	Population Assessment of Tobacco and Health Study (PATH)	USA	1 2013-2015	5762	Ever e-cigarette use (Baseline)	Never e-cigarette, never tobacco users	Tobacco initiation	OR: 4.0 (95% CI: 2.60-6.10)	race/ethnicity, sex, age, education, household smoking rules, and living with someone who smokes cigarettes.
						Past 30-day e-cigarette use (Baseline)		Tobacco initiation	OR: 6.6 (95% CI: 3.7-11.8)	
						Ever e-cigarette use (Baseline)		Current tobacco smoker	OR: 2.5 (95% CI: 0.6-10.9)	
						Past 30-day e-cigarette use (Baseline)		Current tobacco smoker	OR: 8.0 (95% CI: 2.8-22.7)	
Miech, 2017[52]	Prospective Cohort School-based	Monitoring the Future study	USA	1.12 2015-2016	246	Past 30-day e-cigarette use (Baseline)	No past 30-day e-cigarette use, never tobacco users	Tobacco initiation	RR: 4.78 (95% CI: 1.91-11.96)	binge drinking, alcohol use, marijuana use, sex, ethnicity
Morgenstern, 2018[53]	Cluster randomized study School-based		Germany	0.5 2015-2016	2186	Ever e-cigarette use (Baseline)	Never e-cigarette, never tobacco users	Tobacco initiation	RR: 2.18 (95% CI: 1.68-2.83)	Sex, age, state, school, immigration status, parental education, SES, personality factors, substance use (alcohol, binge drinking, cannabis consumption, other illegal drugs)
Penzes, 2018[54]	Cluster randomized control trial School-based		Romania	0.5 2014-2015	707	Ever e-cigarette use (Baseline)	Never e-cigarette, never tobacco users	Tobacco initiation	OR: 3.57 (95% CI: 1.96-6.49)	Sex, age, waterpipe, intervention

Primack, 2015[55]	Prospective Cohort Population-based	Dartmouth Media Advertising and Health Study	USA	1 2012-2014	694	Ever e-cigarette use (Baseline)	Never e-cigarette, never tobacco users	Tobacco initiation	OR: 8.3 (95% CI: 1.2-58.6)	Age, sex, ethnicity, maternal education, sensation seeking, parental and peer smoking
Primack, 2018[56]	Prospective Cohort Population-based	Growth from Knowledge sample	USA	1.5 2013-2014	915	Ever e-cigarette use (Baseline)	Never e-cigarette, never tobacco users	Tobacco initiation	OR: 6.82 (95% CI: 1.65-28.25)	Age, Sex, Ethnicity, relationship status, living situation, yearly household income, education, self-esteem, sensation seeking, rebelliousness
Spindle, 2017[57]	Prospective Cohort College-based	Spit for Science (S4S) project	USA	1 2014-2015	2316	Ever e-cigarette use (Baseline), 153	Never e-cigarette, never tobacco users	Tobacco initiation	OR: 3.37 (95% CI: 1.91-5.94)	Sex, age, ethnicity, depression, anxiety, urgency, premeditation, perseverance, sensation seeking, stressful life events, peer deviance, other product use
						Ever e-cigarette use (Baseline)		Current tobacco smoker	OR: 3.30 (95% CI: 1.20-9.05)	
						Past 30-day e-cigarette use (Baseline)		Tobacco initiation	OR: 3.41 (95% CI: 1.57-7.41)	
						Past 30-day e-cigarette use (Baseline)		Current tobacco smoker	OR: 1.15 (95% CI: 0.15-9.06)	

Treur, 2018[58]	Prospective Cohort School-based	Two Dutch cohorts (Cohort I and Tr&nds study cohort)	Netherlands	0.5 2014-2015	2100	Ever e-cigarettes with Nicotine (Baseline)	Never e-cigarette with nicotine	Tobacco initiation	OR: 11.90 (95% CI: 3.36-42.11)	Sex, age, education, propensity to smoke
Watkins, 2017[59]	Prospective Cohort Population-based	Population Assessment of Tobacco and Health Study (PATH)	USA	0.5 2014-2015	9909	Ever e-cigarette use (Baseline)	Never e-cigarette, never tobacco users	Tobacco initiation	OR: 2.99 (95% CI: 1.98-4.53)	female, age, race/ethnicity, parental educational level, urban residence, sensation seeking, alcohol ever use, living with tobacco user, notice of cigarette warning labels, tobacco advertising receptivity, and summer season
								Current tobacco smoker	OR: 2.12 (95% CI: 1.11-4.03)	
Wills, 2017[60]	Prospective Cohort School-based		USA	1 (2013-2014)	1070	Ever e-cigarette use (Baseline)	Never e-cigarette users, never smokers	Tobacco initiation	OR: 2.87 (95% CI: 2.03-4.05)	Age, gender, ethnicity, parental education, parental support and rebelliousness.

6.3.3 Risk of bias within studies

Of the 24 articles included in this study, when assessing the risk of bias within studies using a modified Newcastle Ottawa Scale for cohort studies[32] (Appendix 1) 20 were assessed as having a low risk of bias and 4 as high risk of bias. The main areas where points were lost were in terms of the ascertainment of exposure where the majority of studies had written or online self-reports, length of follow-up (minimum 1 year) and adequacy of follow up (Table 6.2).

Table 6.2: Risk of bias within studies

Article	Selection (4 points)	Comparability (1 point)	Outcome (3 points)	Risk of Bias
Aleyan, 2018[29]	3	1	2	Low
Barrington, 2016[28]	3	1	3	Low
Barrington, 2018[39]	3	1	2	Low
Berry, 2019[40]	3	1	3	Low
Chien, 2019[41]	3	1	3	Low
Conner, 2018[42]	3	1	3	Low
Conner, 2019[43]	3	1	3	Low
East, 2018[44]	3	1	1	High
Hammond, 2017[45]	4	1	2	Low
Kinnunen, 2019[46]	3	1	3	Low
Kintz, 2019[47]	4	1	2	Low
Leventhal, 2015[48]	3	1	2	Low
Loukas, 2018[49]	3	1	3	Low
Lozano, 2017[50]	4	1	2	Low
MacMillen, 2019[51]	4	1	3	Low
Miech, 2017[52]	3	1	3	Low
Morgenstern, 2018[53]	1	1	1	High
Penzes, 2018[54]	2	1	1	High
Primack, 2015[55]	3	1	3	Low
Primack, 2018[56]	3	1	3	Low
Spindle, 2017[57]	3	1	2	Low
Treur, 2018[58]	3	1	1	High
Watkins, 2017[59]	4	1	2	Low
Wills, 2017[60]	4	1	3	Low

6.3.4 Synthesis of results

Ever e-cigarette use leading to tobacco initiation

The longitudinal relationship between ever e-cigarette use at baseline and conventional tobacco smoking initiation at follow-up was assessed by 16 of the final studies.[28,39-44,48,49,51,54-57,59,60] The pooled odds ratio of this relationship using a random effects model was statistically significant with individuals who ever used e-cigarettes at baseline being OR=3.28 times more likely (95% CI: 2.74-3.92; I^2=62.91) to report the initiation of conventional tobacco smoking at follow-up (Figure 6.2). However, upon visual inspection of the funnel plot (Figure 6.3), there was a slight right skew at the base of the funnel plot suggesting potential for publication bias. However, when we tested for the potential presence of publication bias using Egger's regression test (P-value 2-tailed = 0.33 > 0.05), publication bias was not statistically significant.

Ever e-cigarette use leading to current tobacco use

A total of seven studies examined the longitudinal association between e-cigarette use at baseline and current conventional tobacco smoking (past 30-day conventional tobacco use) at follow-up.[39,40,43,46,51,57,59] A statistically significant association was found, with baseline ever e-cigarette users being OR=2.37 times more likely (95% CI: 1.48-3.77; I^2=78.07) to become current tobacco users at follow-up compared to never e-cigarette and conventional tobacco users (Figure 6.4). When examining for potential publication bias using the funnel plot (Figure 6.5), we noted the studies were right skewed. This was confirmed with Egger's regression test (p-value for 2-tailed test = 0.0049 < 0.05). The Duval and Tweedie's trim and fill methodology was used to adjust for potential publication bias with the new effect measure using a random effects model being OR=1.89, 95% CI: 1.34-2.66; Q-Value = 28.43. Three studies were trimmed and added to the left of the mean (Table 6.3, Figure 6.6).

Study name	Sample Size	Statistics for each study			Forest Plot
		Odds ratio	95% CI	p-value	Odds ratio and 95% CI
Barrington, 2016[28]	298	4.29	1.84-10.00	< 0.01	
Barrington, 2018[39]	6258	4.57	3.59-5.82	< 0.01	
Berry, 2019[40]	6123	4.09	2.97-5.63	< 0.01	
Chien, 2019[41]	12,954	2.14	1.66-2.75	< 0.01	
Conner, 2018[42]	1726	4.06	2.94-5.60	< 0.01	
Conner, 2019[43]	3994	2.78	2.20-3.51	< 0.01	
East, 2018[44]	923	10.57	3.33-33.53	< 0.01	
Leventhal, 2015[48]	2530	1.75	1.10-2.78	0.02	
Loukas, 2018[49]	2558	2.26	1.35-3.77	< 0.01	
MacMillen, 2019[51]	5762	4.00	2.61-6.13	< 0.01	
Penzes, 2018[54]	707	3.57	1.96-6.50	< 0.01	
Primack, 2015[55]	694	8.30	1.19-58.00	0.03	
Primack, 2018[56]	915	6.82	1.65-28.22	0.01	
Spindle, 2017[57]	2316	3.37	1.91-5.94	< 0.01	
Watkins, 2017[59]	9909	2.99	1.98-4.52	< 0.01	
Wills, 2017[60]	1070	2.87	2.03-4.05	< 0.01	
Pooled random effects estimate		3.28	2.74-3.92	< 0.01	

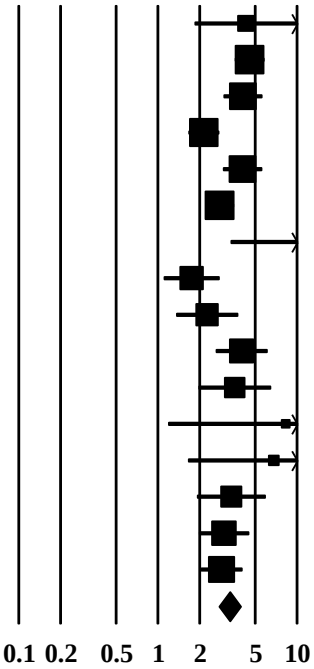

Figure 6.2: Random effects model examining the longitudinal association between ever e-cigarette use at baseline and subsequent tobacco initiation at follow-up

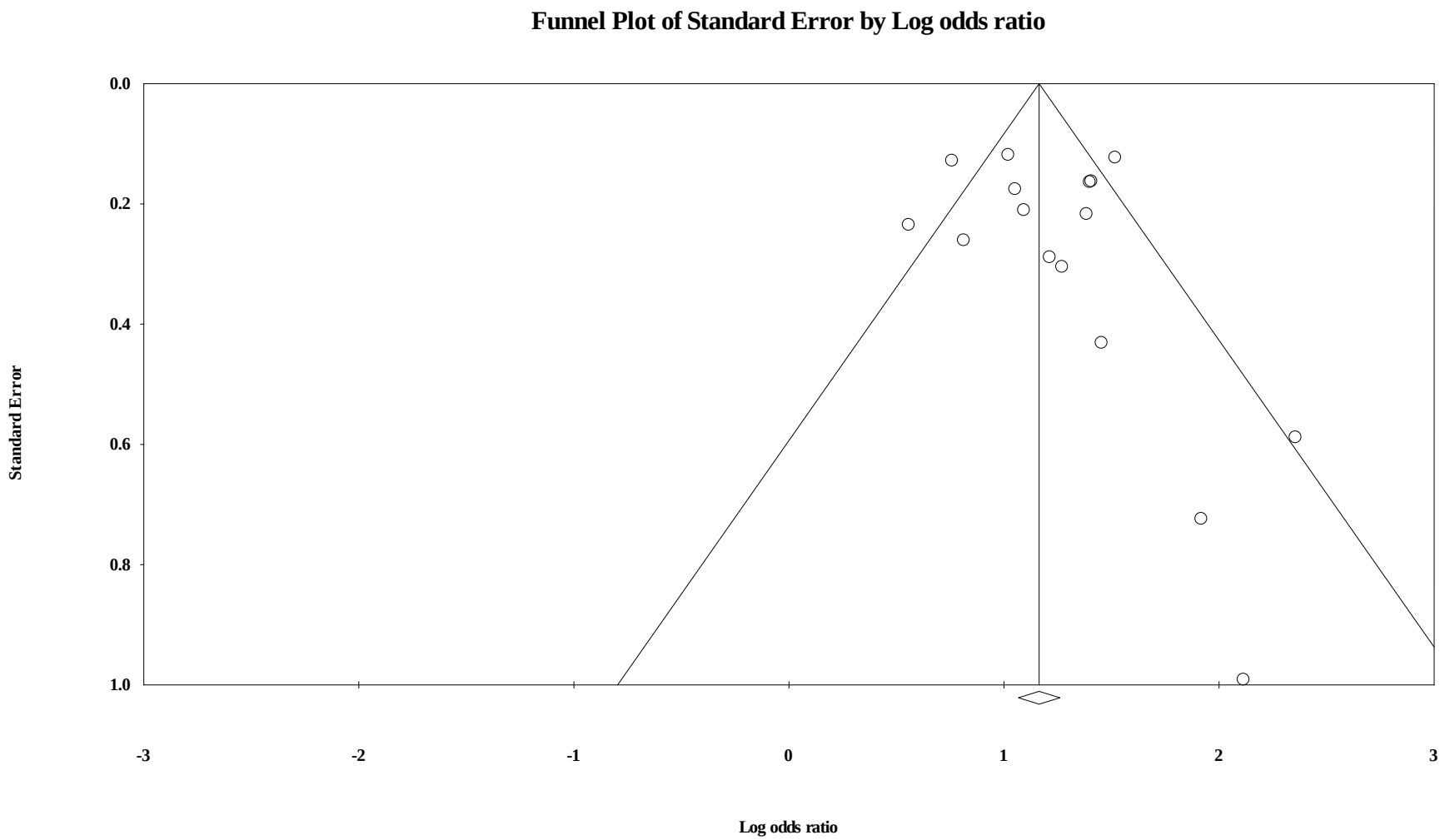

Figure 6.3: Funnel plot of standard error by log odds ratio; ever e-cigarette use at baseline and conventional tobacco initiation at follow-up

Study name	Sample Size	Statistics for each study			Forest Plot
		Odds ratio	95% CI	p-value	Odds ratio and 95% CI
Barrington, 2018[39]	6258	3.51	1.97-6.25	< 0.01	
Berry, 2019[40]	6123	2.75	1.60-4.73	< 0.01	
Conner, 2019[43]	3994	1.27	1.17-1.39	0.03	
MacMillen, 2019[51]	5762	2.50	0.59-10.66	0.215	
Spindle, 2017[57]	2316	3.30	1.20-9.06	0.02	
Watkins, 2017[59]	9909	2.12	1.11-4.04	0.02	
Kinnunen, 2019[46]	1923	2.92	1.09-7.84	0.03	
Pooled random effects estimate		2.37	1.48-3.77	< 0.01	

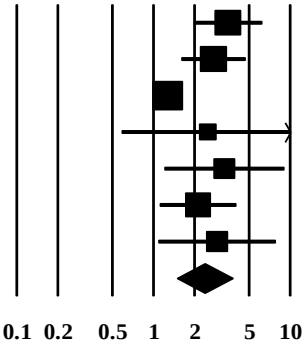

Figure 6.4: Random effects model examining the longitudinal association between ever e-cigarette use at baseline and subsequent current (past 30-day) tobacco use at follow-up

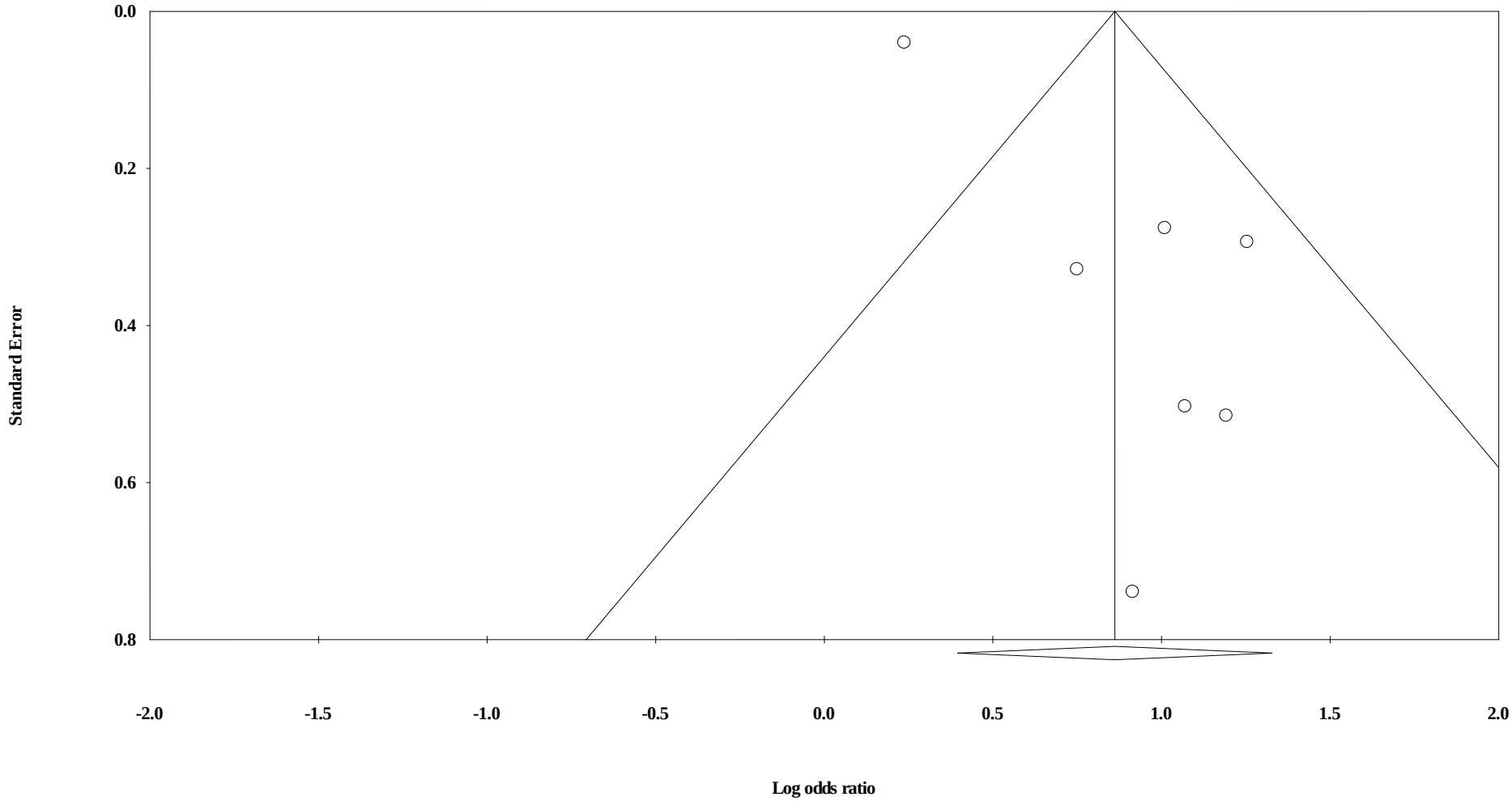

Figure 6.5: Funnel plot of standard error by log odds ratio; ever e-cigarette use at baseline and current tobacco use at follow-up

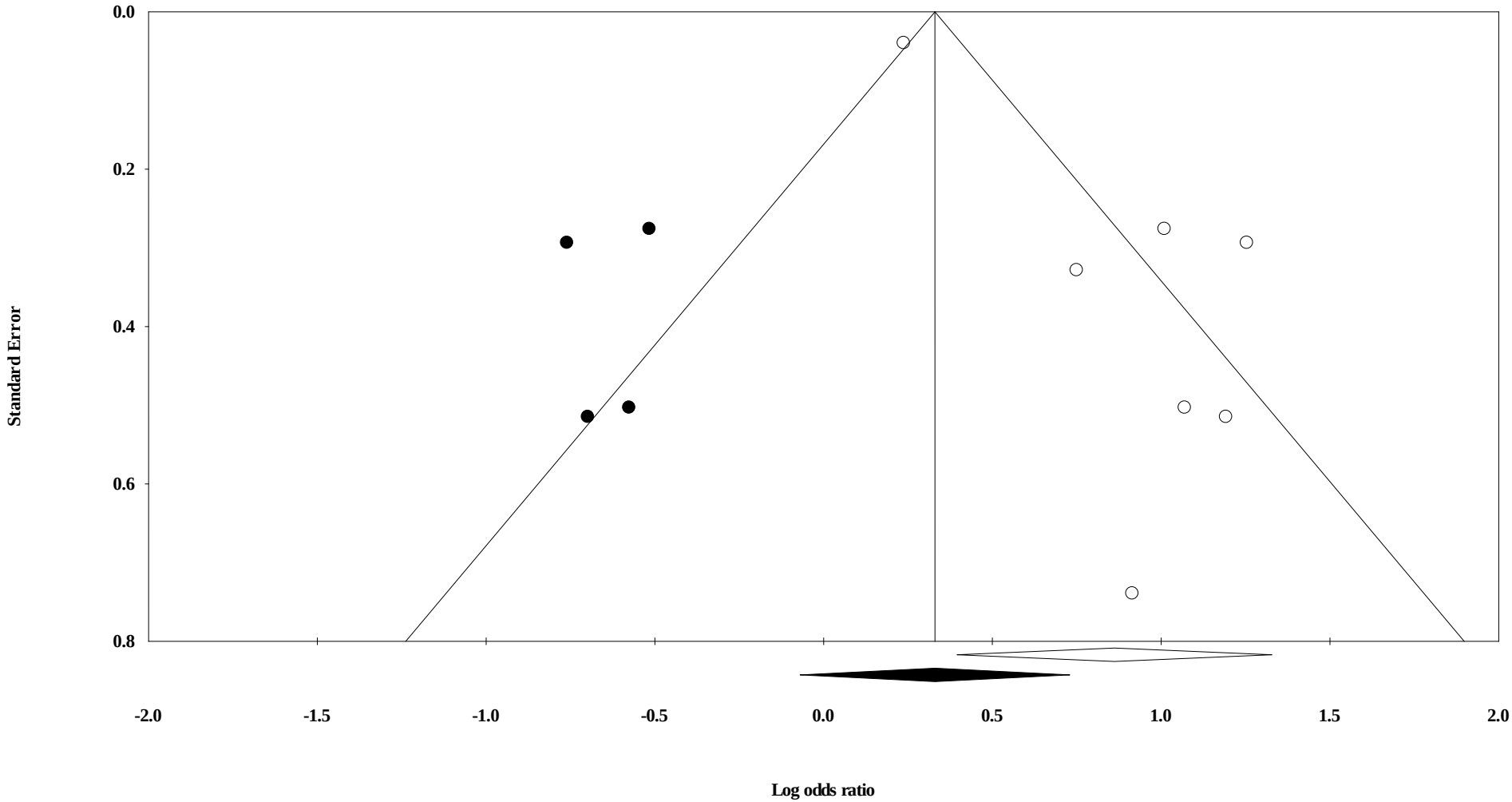

Figure 6.6: Funnel plot of standard error by log odds ratio; ever e-cigarette use at baseline and current tobacco use at follow-up with Duval Trim and Fill correction (studies in black)

Table 6.3: Duval and Tweedie's trim and fill adjustment to effect estimate between ever e-cigarette use at baseline and current tobacco use at follow-up using a random effects model

		Fixed Effects			Random Effects			Q Value
	Studies Trimmed	Point Estimate	Lower Limit	Upper Limit	Point Estimate	Lower Limit	Upper Limit	
Observed values		1.33852	1.24023	1.44460	2.36701	1.48480	3.77341	27.35872
Adjusted values	3	1.32989	1.23358	1.43372	1.88644	1.33930	2.65710	28.43436

6.3.5 Additional analysis

Ever e-cigarette use leading to tobacco initiation – Subgroup by follow-up time

When stratifying baseline ever e-cigarette use and follow-up tobacco initiation by follow-up time, the association remained significant at each follow-up period; 6 months (n=3, OR=3.52, 95% CI: 1.50-8.31; I^2=79.1), 1 year (n=7, OR=3.77, 95% CI: 3.21-4.42; I^2=15.05), 1.5 years (n=3, OR=3.26, 95% CI: 1.79-5.93; I^2=36.01) and 2 years (n=3, OR=2.86, 95% CI: 2.04-4.02; I^2=79.42). While the overall association using the random effects model became OR=3.56 (95% CI: 3.10-4.09; I^2=62.91) when accounting for follow-up time (Figure 6.7).

Ever e-cigarette use leading to current tobacco use – Subgroup by follow-up time

When examining the longitudinal association between ever e-cigarette use at baseline and current tobacco use at follow up by conducting a subgroup analysis by follow-up time, the association persisted at 1 year (n=4, OR=2.85, 95% CI: 1.94-4.17; I^2=0.00) and at 2 years (n=3, OR=1.98, 95% CI: 1.03-3.80; I^2=80.50). Overall, the association using the random effects model became OR=2.60 (95% CI: 1.87-3.61, I^2=78.07) when accounting for follow-up time (Figure 6.8).

Study name	Sample Size	Follow-up (Years)	Statistics for each study			Forest Plot
			Odds ratio	95% CI	p-value	Odds ratio and 95% CI
East, 2018[44]	923	0.5	10.57	3.33-33.53	< 0.01	
Leventhal, 2015[48]	2530	0.5	1.75	1.10-2.78	0.02	
Penzes, 2018[54]	707	0.5	3.57	1.96-6.50	< 0.01	
0.5 year follow-up effects estimate			3.52	1.50-8.31	< 0.01	
Barrington, 2018[39]	6258	1.0	4.57	3.59-5.82	< 0.01	
Conner, 2018[42]	1726	1.0	4.06	2.94-5.60	< 0.01	
MacMillen, 2019[51]	5762	1.0	4.00	2.61-6.13	< 0.01	
Primack, 2015[55]	694	1.0	8.30	1.19-58.00	0.03	
Spindle, 2017[57]	2316	1.0	3.37	1.91-5.94	< 0.01	
Watkins, 2017[59]	9909	1.0	2.99	1.98-4.52	< 0.01	
Wills, 2017[60]	1070	1.0	2.87	2.03-4.05	< 0.01	
1-year follow-up effects estimate			3.76	3.21-4.42	< 0.01	
Barrington, 2016[28]	298	1.5	4.29	1.84-10.00	< 0.01	
Loukas, 2018[49]	2558	1.5	2.26	1.35-3.77	< 0.01	
Primack, 2018[56]	915	1.5	6.82	1.65-28.22	0.01	
1.5-year follow-up effects estimate			3.26	1.79-5.93	< 0.01	
Berry, 2019[40]	6123	2.0	4.09	2.97-5.63	< 0.01	
Chien, 2019[41]	12,954	2.0	2.14	1.66-2.75	< 0.01	
Conner, 2019[43]	3994	2.0	2.78	2.20-3.51	< 0.01	
2-year follow-up effects estimate			2.86	2.04-4.02	< 0.01	
Overall effects estimate			3.56	3.10-4.09	< 0.01	

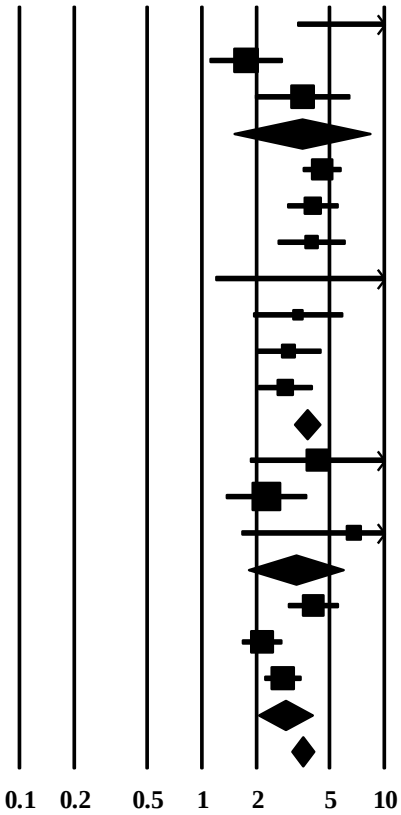

Figure 6.7: Sub-group analysis by length of follow-up (0.5, 1.0, 1.5 and 2.0 years) using a random effects model examining the longitudinal association between ever e-cigarette use at baseline and tobacco initiation at follow-up

Study name	Sample Size	Follow-up	Statistics for each study			Forest Plot
			Odds ratio	95% CI	p-value	Odds ratio and 95% CI
Barrington, 2018[39]	6258	1	3.51	1.97-6.25	< 0.01	
MacMillen, 2019[51]	5762	1	2.50	0.59-10.66	0.21	
Spindle, 2017[57]	2316	1	3.30	1.20-9.06	0.02	
Watkins, 2017[59]	9909	1	2.12	1.11-4.04	0.02	
1-year follow-up effects estimate			2.85	1.94-4.17	< 0.01	
Berry, 2019[40]	6123	2	2.75	1.60-4.73	< 0.01	
Conner, 2019[43]	3994	2	1.27	1.17-1.37	< 0.01	
Kinnunen, 2019[46]	1923	2	2.92	1.09-7.84	< 0.01	
2-year follow-up effects estimate			1.98	1.03-3.79	0.04	
Overall effects estimate			2.60	1.87-3.80	< 0.01	

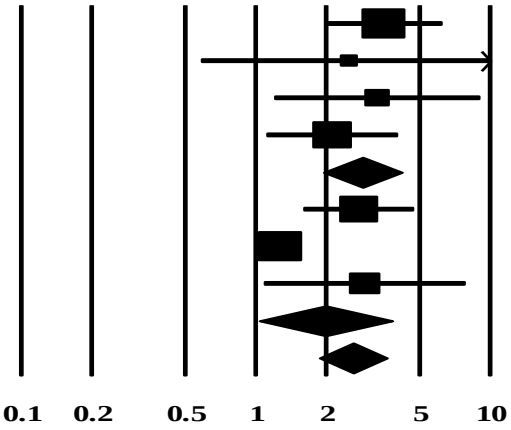

Figure 6.8: Sub-group analysis by length of follow-up (1.0, and 2.0 years) using a random effects model examining the longitudinal association between ever e-cigarette use at baseline and current tobacco use at follow-up

6.4 Discussion

E-cigarette use is a growing public health concern, and there are different proposed hypotheses for how e-cigarette use leads to conventional tobacco initiation (addiction, accessibility and experience hypotheses).[30] This systematic review and meta-analysis pooled data from 17 studies, 16 of which examined the longitudinal relationship between ever e-cigarette use at baseline and conventional tobacco smoking initiation at follow-up, with a control group consisting of e-cigarette and tobacco naïve participants[28,39-44,48,49,51,54-57,59,60] and data from seven studies was pooled examining the effect of baseline ever e-cigarette use on follow-up current tobacco use.[39,40,43,46,51,57,59] We used the most adjusted measures of association for the pooled meta-analysis to determine the most conservative effect measure accounting for the most variability possible in the outcome measures (tobacco initiation and current tobacco use).

Our results indicated statistically significant associations between ever e-cigarette use at baseline and tobacco initiation at follow up (Pooled OR=3.28, 95% CI: 2.74-3.92; I^2=62.91) with moderate heterogeneity. Follow-up time contributed to this heterogeneity and we conducted a subgroup analysis. All time periods remained statistically significant and our results are consistent with previous studies.[45,47,61,62] Interestingly, longer follow up periods had lower effect estimates. We found further evidence that ever e-cigarette use at baseline was a predictor of current tobacco use at follow up (Pooled OR=1.89, 95% CI: 1.34-2.66; Q=28.43) compared to tobacco and e-cigarette naïve respondents. These findings are troubling as there is evidence that baseline e-cigarette use increases susceptibility to conventional tobacco by both increased curiosity and willingness to initiate.[63] Moreover, individuals susceptible to e-cigarettes have an increased risk of initiating conventional tobacco use after e-cigarette initiation.[64] This study used ever e-cigarette use as the exposure of interest, and our findings show a relationship with tobacco initiation, this could mean similar to cigarettes with an estimated 69% of tobacco experimenters becoming temporarily a daily smoker after just 1 cigarette,[65] e-cigarette vapor may possibly have similar effects that warrant further study.

The e-cigarette use behaviour (ever use vs. past 30-day use) was an area we were unable to conduct a meta-analysis for, however the studies included in this study indicate that past 30-day e-cigarette users who were tobacco naïve were at greater risk of tobacco initiation[29,45,51,52] with a

relative risk estimate of 4.78 (95% CI: 1.91-11.96)[52] and adjusted odds ratios ranging from 2 to 6.[29,45,51,57] However, there was significant heterogeneity in the exposure assessment therefore we did not conduct a meta-analysis. We additionally wanted to examine the effects of e-cigarette use by sex to see if there are any differences in conventional tobacco initiation when comparing males to females however, we did not find any study stratifying based on sex, most were simply accounting for biological sex as a covariable, suggesting a gap in the literature that needs to be investigated. When examining the relationship between ever e-cigarette use at baseline and tobacco initiation at follow-up, we did not find evidence of small study effects or publication bias (Figure 6.3), and Egger's test was not significant. We did have moderate heterogeneity though I^2=62.91. These findings can be attributed to several factors such as length of follow-up, sample size, sociodemographic factors (geographical location, age, sex), and not having a timeframe of "ever e-cigarette use". Furthermore, to attain the most conservative estimates we used the estimates from the most adjusted models reported. To best address heterogeneity in our meta-analysis, we used individuals defined as ever e-cigarette users who were never tobacco smokers as the baseline population. Our sub-group analysis showed high heterogeneity at 6 months and 2 years follow-up (I^2=79.1 and 79.42 respectively), but low heterogeneity at 1 year (I^2=15.05) and at 1.5 years follow-up (I^2=36.01) The results of ever e-cigarette use and future current conventional tobacco use had high heterogeneity (I^2=78.07) and there was evidence of either small study size or publication bias requiring adjustment (Figure 6.6 and Table 6.3). The funnel plot was right skewed towards the base (Figure 6.5), but when conducting subgroup analysis, similar to with tobacco initiation, the heterogeneity at 1 year follow up was low (I^2=0.00), while at 2 years was high (I^2=80.50). These findings suggest future studies should account for follow-up time in the analysis when examining the effect of e-cigarette use on conventional tobacco behaviours and there may be additional factors influencing tobacco related behaviours at longer follow-up times. Two articles that examined the relationship between baseline ever e-cigarette use and tobacco initiation at follow-up had very wide confidence intervals[44,55] but removing these studies did not significantly influence the final effect measure (Appendix 2).

Health promotion and education campaigns, especially aimed at youth and young adults need to better increase awareness of the potential harms associated with e-cigarette use and their role as tobacco initiation devices, as currently there are many positive attitudes, beliefs and societal

norms surrounding e-cigarettes[9-19] and they are not stigmatized like tobacco. Furthermore, policy makers need to restrict e-cigarette marketing and use similar to tobacco policies as there is evidence, they are being used to circumvent effective existing tobacco policies.[65]

Study's strengths and limitations:

Strengths of this study included using a robust, reproducible and validated methodology, having sufficient recent longitudinal studies included to conduct a meta-analysis with a temporal component and providing up to date information and insights into an area of research that has conflicting opinions. All the studies included in our meta-analysis used tobacco and e-cigarette naïve control groups, and assessed e-cigarette use at baseline without having any ever tobacco users. Despite trying to standardize the exposure and outcome measurements, different studies have different adjustments for the outcome of interest (tobacco initiation or current tobacco initiation). In addition, the follow-up periods were different for different studies, but we tried to account for this in our subgroup analysis. Additionally, results are not necessarily generalizable because there are studies from different regions of the world. Most studies assessed the exposure and the outcome through self-reported questionnaires which may introduce bias. Finally, certain studies had a low number of e-cigarette users or conventional tobacco initiation which may result in over or underestimating the measure of effect in pooled analysis, however, our results are consistent with recently published literature and a previous meta-analysis.

6.5 Conclusions

E-cigarettes are a growing public health concern. Our results suggest that there are potential future implications of the continued growth in e-cigarette uptake especially among youth as we found significant associations between baseline ever e-cigarette use and both conventional tobacco initiation and current tobacco use at follow-up. These findings suggest there is potentially an “intermediary” step in conventional tobacco uptake which could possibly lead to a new delayed-onset tobacco epidemic in the future leading to increased and unforeseen morbidity and mortality, circumventing effective tobacco cessation and control policies and educational initiatives. Current initiatives need to incorporate all smoking related behaviours, and not just focus on tobacco cessation as they are interlinked and share common risk factors as well as unique factors. Future research incorporating the dose of e-cigarettes, sex-based differences and nicotine content would be of immense value in characterizing the potential risks associated with e-cigarette use.

6.6 References

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Appendix 1 – Modified Newcastle Ottawa Scale and Scoring

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of one star can be given for Comparability

Selection

1) Representativeness of the exposed cohort
   a) truly representative of the average _____ (describe) in the community □
   b) somewhat representative of the average _____ in the community □
   c) selected group of users eg nurses, volunteers
   d) no description of the derivation of the cohort
2) Selection of the non exposed cohort (Control Group)
   a) drawn from the same community as the exposed cohort □
   b) drawn from a different source
   c) no description of the derivation of the non exposed cohort
3) Ascertainment of exposure
   a) secure record (eg surgical records or verified) □
   b) structured interview □
   c) written self report
   d) no description
4) Demonstration that outcome of interest was not present at start of study
   a) yes □
   b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis (i.e. analysis of covariables)
   a) study controls for age, sex, other tobacco products (select the most important factor) □
   b) study controls for any additional factor □ (This criteria could be modified to indicate specific control for a second important factor.)

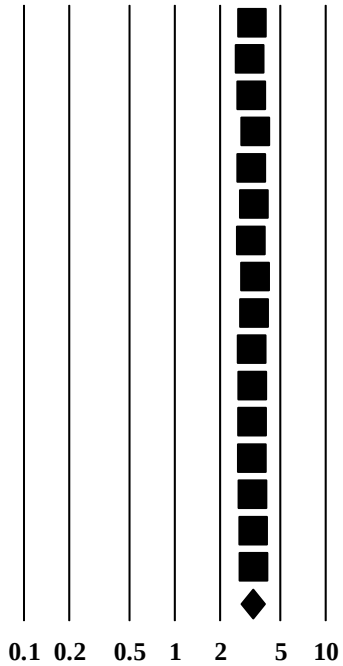
Outcome

1) Assessment of outcome
   a) independent blind assessment □
   b) record linkage □
   c) self report □
   d) no description
2) Was follow-up long enough for outcomes to occur **(Minimum 1-year)**
   a) yes (select an adequate follow up period for outcome of interest) □
   b) no
3) Adequacy of follow up of cohorts
   a) complete follow up - all subjects accounted for □
   b) subjects lost to follow up unlikely to introduce bias - small number lost - > **20** % (select an adequate %) follow up, or description provided of those lost) □
   c) follow up rate < **80**% (select an adequate %) and no description of those lost
   d) no statement

Low Risk of Bias: 3 or 4 stars in selection domain AND 1 star in comparability domain AND 2 or 3 stars in outcome/exposure domain
Moderate Risk of Bias: 2 stars in selection domain AND 1 star in comparability domain AND 2 or 3 stars in outcome/exposure domain
High Risk of Bias: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain

Appendix 2 – Effect of one study removed; ever e-cigarette use and tobacco initiation

Study name	Sample Size	Statistics with study removed			Forest Plot
		Odds ratio	95% CI	p-value	Odds ratio and 95% CI
Barrington, 2016[28]	298	3.25	2.71-3.91	< 0.01	
Barrington, 2018[39]	6258	3.14	2.64-3.74	< 0.01	
Berry, 2019[40]	6123	3.22	2.66-3.89	< 0.01	
Chien, 2019[41]	12,954	3.42	2.89-4.05	< 0.01	
Conner, 2018[42]	1726	3.22	2.66-3.89	< 0.01	
Conner, 2019[43]	3994	3.35	2.75-4.09	< 0.01	
East, 2018[44]	923	3.20	2.69-3.80	< 0.01	
Leventhal, 2015[48]	2530	3.41	2.87-4.06	< 0.01	
Loukas, 2018[49]	2558	3.36	2.79-4.04	< 0.01	
MacMillen, 2019[51]	5762	3.23	2.68-3.91	< 0.01	
Penzes, 2018[54]	707	3.27	2.71-3.94	< 0.01	
Primack, 2015[55]	694	3.26	2.72-3.90	< 0.01	
Primack, 2018[56]	915	3.25	2.71-3.89	< 0.01	
Spindle, 2017[57]	2316	3.28	2.72-3.96	< 0.01	
Watkins, 2017[59]	9909	3.31	2.73-4.01	< 0.01	
Wills, 2017[60]	1070	3.33	2.74-4.04	< 0.01	
Overall random effects estimate		3.28	2.74-3.92	< 0.01	



This appendix details the influence of each study on the association between baseline ever e-cigarette use and follow up tobacco initiation.

CHAPTER 7: CONCLUSION

The purpose of this thesis was to examine Canadian smoking related behaviours, specifically the different types of nicotine products available (conventional tobacco cigarettes, flavoured tobacco products and e-cigarettes), their prevalence, determinants, negative health outcomes and their dynamic complementarity.

This thesis has addresses priority research areas that have a dearth of knowledge or lack of consensus and incorporates sex and gender considerations where applicable.

Chapter 3 examined the prevalence and determinants of flavoured tobacco among youth, a rapidly growing phenomenon.

Chapter 4 assessed the prevalence and identified determinants associated with conventional tobacco cigarette use among the Canadian LGB community. Lesbians and bisexuals were identified as a vulnerable population disproportionately affected by the tobacco epidemic.

Chapter 5 assessed the prevalence of COPD by past 30-day e-cigarette use among individuals from Ontario, British Columbia, Nova Scotia and the Northwest Territories, and quantified the association between e-cigarette use and COPD and identified sex-based effects modification.

Chapter 6 was a systematic review and meta-analysis which found the use of e-cigarettes leads to conventional tobacco initiation over time using the most up to date data from published longitudinal studies.

7.1 Major findings

This thesis investigated various aspects of smoking related behaviours. From identifying determinants and risk profiles among vulnerable populations (Canadian high school students for flavoured tobacco and the Canadian LGB population for conventional tobacco smoking), health outcomes due to novel nicotine delivery devices (the association between e-cigarettes and COPD) and what the relationship is between e-cigarette use and conventional tobacco initiation. Taken together, this thesis discusses aspects related to smoking behaviours in the epidemiology, health promotion and policy implications.

Chapter 3 (*Prevalence and characteristics of flavoured tobacco use among students in grades 10 through 12)* provided a framework to identify individuals at highest risk of flavoured tobacco use, which was purported to be easier to initiate, a safer alternative to conventional tobacco cigarette and a tobacco cessation device.[1] A weighted logistic regression analysis was carried out using the national, generalizable survey the Youth Smoking Survey (YSS) (2012-2013), and we developed our own flavoured tobacco use outcome variable (menthol cigarette or flavoured little cigar or cigarillo or flavoured cigar or flavoured tobacco in a water-pipe [hookah]) that was since adopted by the Canadian Student Tobacco, Alcohol and Drugs Survey (CSTADS, which is the continuation of the YSS) with the addition of smokeless tobacco and is being used in flavoured tobacco surveillance. Independent variables explored in this study included sex, grade, ethnicity, number of friends who smoke, sibling smokers, parent/guardian who smoke and weekly personal spending. Interestingly parental/guardian smoking was not significant upon logistic regression analysis, this suggests that adolescents are more influenced by their age group at least in terms of risky behaviours. Furthermore, contrary to studies from the US, ethnic differences among students in grade 10-12 was barely significant with individuals of Asian descent having 35% lower rates of flavoured tobacco use compared to students reporting White as their ethnic background. Males had a stronger association with flavoured tobacco use which may be attributed to increased risk taking behaviours and easier accessibility to purchase flavoured tobacco cigarettes. The strongest association with flavoured tobacco use in our study was situational factors, in this case peer use (number of friends and siblings who smoke). Furthermore, contrary to most population based studies that find lower socioeconomic status leads to worse outcomes, in this study students who had more than $100/week in spending

money were more likely to partake in flavoured tobacco use, with a graded increase as weekly spending increased. Since this study was published, the Canadian government has banned all flavoured tobacco as of 2018[2] and the impact of this ban remains to be seen, maybe students will decrease smoking related behaviours or there could be a shift towards electronic cigarettes which have a lot of commonalities with flavoured tobacco and are marketed similarly.

Chapter 4 (*Sexual orientation and smoking preferences results from a population-based survey in Canada 2009-2014*) explored whether sexual orientation is independently associated with conventional tobacco smoking, and identified and characterized the Canadian lesbian/gay and bisexual (LGB) community, results of which provided important sex and gender implications when it comes to conventional tobacco use. To the best of our knowledge, this was the first Canadian population-based study examining the relationship between sexual orientation and conventional tobacco use and this is partially attributed to the low prevalence of self-reported sexual minorities, thus we merged several survey cycles to create a large enough sample to analyze. Overall, the prevalence of conventional tobacco users was higher among all sexual minority groups compared to heterosexuals. This is unsurprising as they are a highly vulnerable population that has been targeted by the tobacco industry. A major finding was that the term "LGB" is not indicative of these unique and heterogenous populations. While the lesbian and gay population was majority male, older, former smokers, highly educated with good mental health, the bisexual population was majority female, young, current smokers, poorly educated and with higher rates of poor mental health. Both populations had different risk profiles for conventional tobacco use and health education and promotion efforts should be tailored appropriately rather than broadly collapsing them into one group. This study used a nominal multinomial regression approach, in other words the outcome variable (smoking status) had three levels (current or past 30-day, former and never smokers). Our final model found differences in smoking status by sexual orientation among biological females but not among biological males which was another interesting finding adding more evidence to the literature. In other words, there was no statistically significant difference in smoking status among males whether they were heterosexual, gay or bisexual. Among biological females though, bisexuals and lesbians were more likely to be current or former rather than never smokers when compared to heterosexual females. This may be partially attributed to the dual disadvantage theory, whereby they are

disadvantaged both due to their biological sex (female) as well as their sexual orientation (bisexual or lesbian).[3]

Chapter 5 (*Examining the prevalence and association between e-cigarette use and chronic obstructive pulmonary disease in Canada: a cross-sectional study*) is a population-based study using data from Ontario, British Columbia, Nova Scotia and the Northwest Territories examining whether an association exists between e-cigarette use and COPD. Furthermore, it adds additional evidence with respect to dual use behaviours. In this chapter we identified COPD as a negative health outcome independently associated with e-cigarettes, adding evidence to existing proposed mechanisms in in vitro and animal studies. This study is exploratory in nature and cross-sectional therefore we cannot infer cause and effect from our results. Interestingly the prevalence of COPD among e-cigarette users was higher than that among conventional tobacco users however, there is significant overlap between the two with the majority of past 30-day e-cigarette users also being dual current tobacco users. This may be due to increased nicotine dependence and exposure or due to switching to reduce tobacco use. The majority of e-cigarette users were in the younger age group, while current tobacco users were in the middle-age group. Sex-based differences were identified in this study and similar to tobacco studies, female past 30-day e-cigarette users reported significantly higher rates of COPD compared to male past 30-day e-cigarette users. In addition, a sex-based effect modifier was significant where female past 30-day e-cigarette users had a more pronounced odds of COPD compared to female non e-cigarette users. While among males the difference based on past 30-day e-cigarette use was still significant, the odds were lower. This may be due to differential nicotine metabolism as female tobacco smokers require less of a dose to develop COPD symptomology and requires further investigation. Our exploratory analysis of dual e-cigarette and tobacco behaviours (dynamic complementarity) found that individuals who are dual users were more likely to report COPD, suggesting that there might be an additive or synergistic effect of using e-cigarettes and conventional tobacco, however as this study is cross-sectional, further studies are required to ascertain this finding.

Chapter 6 (*E-cigarettes as tobacco initiation devices: A systematic review and meta-analysis*) added a temporality component to this thesis and examined the dynamic complementarity between initial e-cigarette use leading to tobacco initiation. As e-cigarettes were introduced

globally in 2007, in order to determine temporality and causality longitudinal studies are required. This chapter addressed this gap by incorporating data from 17 studies which were collected between 2012-2016 and published between 2015-2019. The PRISMA-P guidelines were followed, and pooled meta-analysis indicated that baseline ever e-cigarette use was associated with follow-up conventional tobacco initiation and current (past 30-day) tobacco initiation from a cohort of never-smokers. A major strength of this study is that the control group was consistent (never conventional tobacco users, never e-cigarette users), the exposure was consistent (ever e-cigarette use). One of the issues encountered was follow-up time which varied from six months to two years in the longitudinal studies, as a result a sub-group analysis was conducted incorporating follow-up time and results remained consistent with e-cigarette use remaining associated with follow-up tobacco initiation amongst all the groups.

Figure 7.1 details the major findings of this thesis and how they are inter-connected in addressing the tobacco epidemic from different points of entry which include: 1) identifying determinants of vulnerable populations who are at greater risk of tobacco use; 2) identifying morbidities associated with e-cigarette use; and 3) identifying the relationship between e-cigarette use and the initiation of conventional tobacco smoking. As tobacco use is the leading cause of premature death worldwide[4] and has serious adverse effects such as COPD,[5] which is predicted to be the third leading cause of death worldwide,[6] using a multifaceted approach to address evolving smoking related behaviours and identifying possible health risks is necessary.

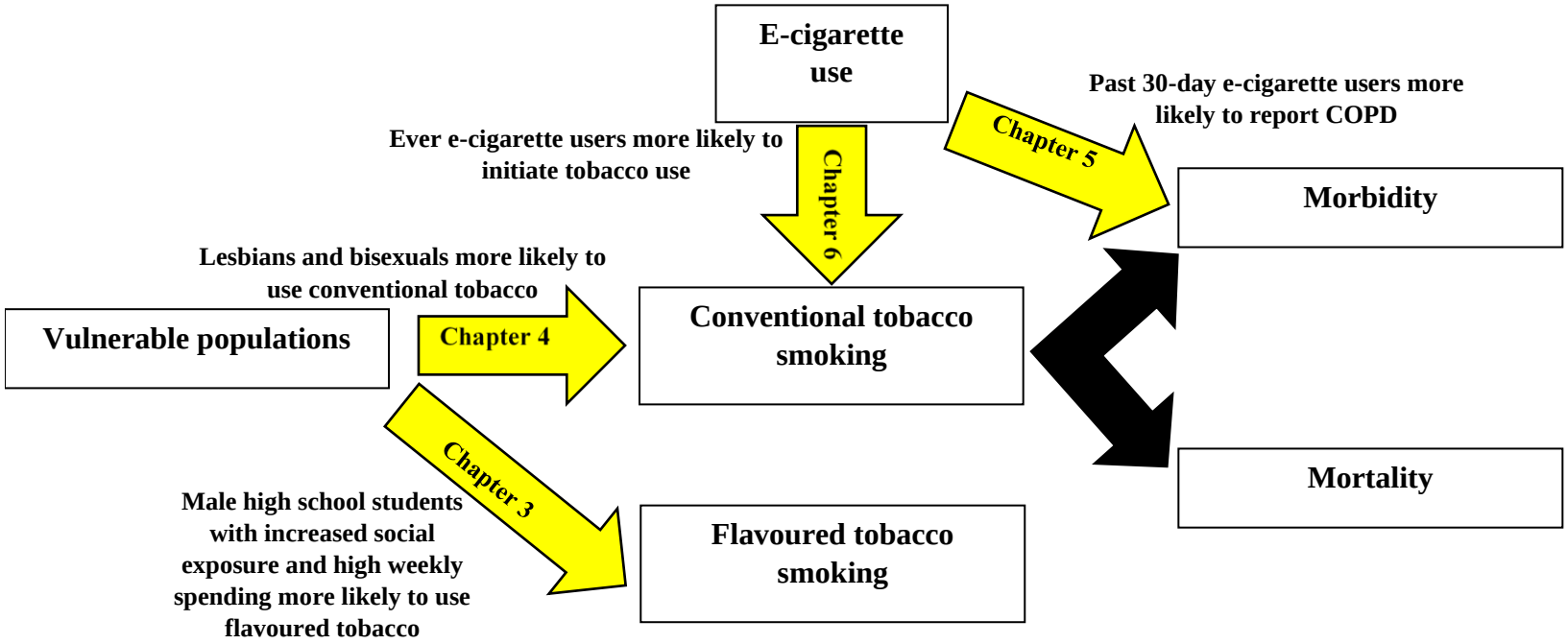


Figure 7.1: Summary of major findings and inter-relatedness of this thesis. Chapter 3 examined determinants of flavoured tobacco smoking among youth. Chapter 4 examined determinants of LGB smoking at the population level. Chapter 5 examined the association between e-cigarette use and COPD. Chapter 6 examined e-cigarettes as conventional tobacco initiation devices. Yellow arrows denote areas examined in this thesis. Black arrows denote known effects of conventional tobacco use.

7.2 Policy implications and future research

Findings from this thesis have implications in health promotion and education strategies, policy planning, evaluation and implementation and future research directions. It is important to note that smoking related behaviours are constantly evolving. In the 2010s flavoured tobacco was the major risky behaviour appealing to youth, but since the ban in 2018, flavoured tobacco has peaked as a smoking related behaviour. Going forward into the 2020s, the unchecked growth of e-cigarettes may lead to a delayed onset neo-tobacco epidemic. Similar strategies to recruit youth and vulnerable populations towards flavoured tobacco use in the past are currently being employed in e-cigarette recruitment. There is evidence of potential health consequences associated with e-cigarettes however, knowledge and perceptions among the general population are lacking. Vision and leadership by public health professionals, in research, health promotion, and education campaigns and in developing and evaluating comprehensive tobacco control and prevention policies incorporating all forms of smoking related behaviours are necessary. Failure to do so may result in e-cigarettes being a tool to circumvent global tobacco control strategies.

In alignment with the new requirements of the Canadian Institute for Health Research, this thesis incorporated sex and gender considerations throughout and found further evidence that they play a key role in conventional tobacco smoking (Chapter 4), and influence health outcomes (Chapter 5). As such, future research examining smoking behaviours by health outcomes and characterizing different sub-populations should incorporate sex and gender considerations where applicable. While the LGB population are sexual minority groups, there is no gender identity variables in national health surveys. As stigmatization continues to decrease, further studies on unique gender identity groups will be worthwhile and better determine what groups are at greater risk and allow health promotion efforts to be tailored accordingly.

Research into e-cigarettes is ongoing and there are a lot of avenues to pursue. One of the major limitations of Chapter 5 was that we were unable to assess the association between past 30-day e-cigarette users who never used conventional tobacco and COPD due to low sample size. As the Canadian population continues to age, more e-cigarette users will enter the younger age groups permitting this association to be tested. Additionally, studies examining e-cigarettes tend to use past 30-day e-cigarette use and/or ever e-cigarette use as indicators. Nicotine content of e-

cigarette use is an important risk factor that has not been strongly studied as of yet and should be assessed in future research. Moreover, there is a need to develop a standardized description of e-cigarette use, a framework like that of tobacco use. With tobacco use the definitions are clear, a never smoker, never smoked, an experimental smoker smoked less than 100 cigarettes in their lifetime and none in the past 30 days, a former smoker smoked more than 100 cigarettes in their lifetime but none in the past 30 days, and a current smoker smoked more than 100 cigarettes in their lifetime but not in the past 30 days. There is no equivalence for e-cigarette use yet, the best measures are ever use and past 30-day use, but magnitude and length of use need to be standardized for future research. An additional area that needs more research is the growth of dual use between e-cigarettes and conventional tobacco use. This thesis shows that dual users had the highest association with COPD. This group is replacing single product users and might potentially have worse morbidity due to increased exposures to nicotine and related content or switching products due to perceived harm reduction. Research needs to be conducted to determine why the sudden growth in dual use, is it a reaction to existing tobacco control policies, social norms or are dual users the most addicted to nicotine and what is the harm reduction potential. Finally, while we documented the association between ever e-cigarette use and tobacco initiation, it would be worthwhile for future research to examine past 30-day e-cigarette use and tobacco initiation as well as what is the association between e-cigarette use and tobacco initiation among males and females to look for any disparities.

7.3 Strengths and limitations

A strength of this thesis is the novelty of tobacco related products under study. As a result, it provides additional insights into smoking related behaviours and the prevalence of alternative tobacco products (flavoured tobacco and e-cigarettes). One of the limitations of this thesis was the amount of data available, whether on the LGB population (Chapter 4), or e-cigarette use (Chapter 5 & 6). To account for limited data from the LGB population we used a pooled approach to maximize the sample size and improve our estimates. With respect to e-cigarette use, the model diagnostics indicated good fits and the findings while exploratory are timely and relevant. In chapter 5 due to data limitations, we were unable to ascertain the association between never smokers who were past 30-day e-cigarette users with COPD, this is due to data and time limitations (e-cigarettes only became available in 2007). E-cigarettes are still a new and developing nicotine delivery system and uptake is mostly by youth and young adults therefore it will require time before chronic diseases and cancer effects can be thoroughly characterized at the population level, however, identifying e-cigarette use behaviours early can help inform public health practices to try and prevent future negative health outcomes. In chapter 6 we did not have sufficient evidence to do a meta-analysis of the longitudinal association between past 30-day e-cigarette use and tobacco initiation. Not many longitudinal studies assessed past 30-day e-cigarette use which might be useful in examining the dose response of e-cigarette exposure, nicotine addiction and future tobacco smoking. Another limitation of chapters 3-5 was using cross-sectional data. We are unable to infer causality only association, but our major findings are either biologically plausible, clinically relevant and/or consistent with previous studies, providing additional evidence in the field of smoking behaviours from a Canadian perspective.

7.4 References

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Portions Fig. 1. Image on page 68

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